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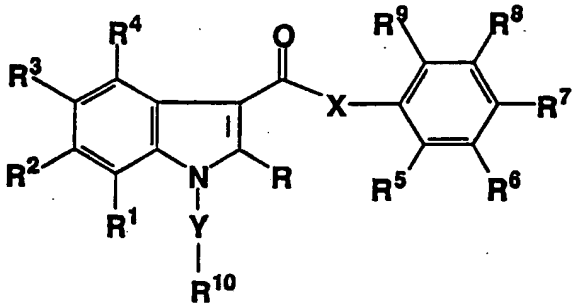

...(I)

(57) Abstract

The present invention provides compounds of formula (I) and pharmaceutically acceptable salts thereof, wherein X is O, NH, N(C_1-C_4 alkyl), C_1-C_4 alkylene, C_2-C_4 alkenylene or C_2-C_4 alkynylene, said alkylene, alkenylene and alkynylene groups being optionally substituted by C_1-C_4 alkyl or aryl; Y is C_1-C_6 alkylene optionally substituted by C_1-C_6 alkyl; R is H, OH, halo, C_1-C_4 alkyl or C_1-C_4 alkoxy; R^1, R^2, R^3 and R^4 are each independently selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, OH, halo and CF_3; one of R^6, R^7 and R^8 is C_1-C_{15} alkyl or a group of the formula -Z(C_1-C_{15} alkyl), -Z(aryl) or -Z(C_3-C_7 cycloalkyl), said alkyl group being optionally interrupted by O, $S(O)_q$, NH or N(C_1-C_6 alkyl), and said alkyl group and the alkyl group of said -Z(C_1-C_{15} alkyl) group being optionally substituted by C_1-C_{10} alkoxy, aryl, C_3-C_7 cycloalkyl or a group of the formula -Z(aryl), and the remainder of R^6, R^7 and R^8 and R^5 and R^9 are each independently selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, halo and halo(C_1-C_4 alkyl); R^{10} is COOH, $COOR^{11}$ or $CONR^{12}R^{13}$; R^{11} is a biolabile ester-forming group; R^{12} and R^{13} are each independently selected from H and C_1-C_4 alkyl; Z is O, $S(O)_q$, NH or N(C_1-C_6 alkyl); q is 0, 1 or 2; and "aryl" used in the definitions of X, R^6, R^7 and R^8, means phenyl optionally substituted by C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl, OH, halo, CF_3, halo(C_1-C_6 alkyl), nitro, amino, C_2-C_6 alkanamido, C_2-C_6 alkanoyl or phenyl: together with pharmaceutical compositions containing, processes for the preparation of and uses of, such compounds.

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INDOLES

This invention relates to indole derivatives which have steroid 5α-reductase inhibitory activity.

More particularly this invention relates to indoles, their preparation and their use as testosterone-5α-reductase inhibitors.

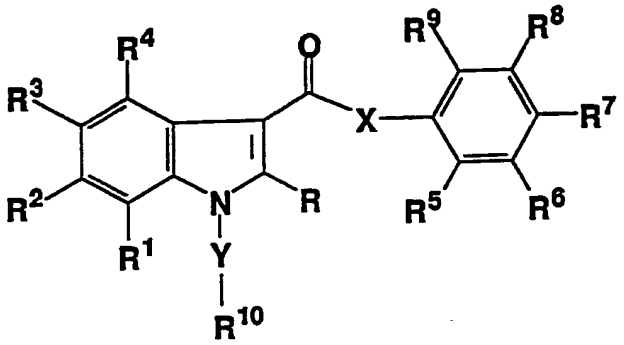
The androgen class of steroidal hormones, which includes testosterone, is responsible for the difference in the physical characteristics of males and females. Of all the organs that produce androgens, the testes produce these hormones in the greatest amounts. Over-production of these hormones in the body results in many undesirable physical manifestations and disease states, e.g. acne vulgaris, alopecia, seborrhoea, female hirsutism, benign prostatic hypertrophy and male pattern baldness.

The principal androgen secreted by the testes is testosterone and it is the primary androgen present in male plasma. The principal mediator of androgenic activity in certain organs such as the prostate and sebaceous gland are the 5α-reduced androgens. Testosterone is therefore the prohormone of 5α-dihydrotestosterone which is formed locally in the above organs by the action of testosterone-5α-reductase. The presence of elevated levels of dihydrotestosterone in many disease states has therefore focussed attention on the synthesis of testosterone 5α-reductase inhibitors.

Testosterone 5α-reductase inhibitors may also be useful in the treatment of human prostate adenocarcinomas.

EP-A-0458207 discloses certain indole derivatives which have testosterone 5α-reductase inhibitory activity.

The present invention provides compounds of the formula:-



....(I)

and pharmaceutically acceptable salts thereof,

wherein X is O, NH, N(C_1-C_4 alkyl), C_1-C_4 alkylene, C_2-C_4 alkenylene or C_2-C_4 alkynylene, said alkylene, alkenylene and alkynylene groups being optionally substituted by C_1-C_4 alkyl or aryl;

Y is C_1-C_6 alkylene optionally substituted by C_1-C_6 alkyl;

R is H, OH, halo, C_1-C_4 alkyl or C_1-C_4 alkoxy;

R^1, R^2, R^3 and R^4 are each independently selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, OH, halo and CF_3;

one of R^6, R^7 and R^8 is C_1-C_{15} alkyl or a group of the formula -Z(C_1-C_{15} alkyl), -Z(aryl) or -Z(C_3-C_7 cycloalkyl), said alkyl group being optionally interrupted by O, $S(O)_q$, NH or N(C_1-C_6 alkyl), and said alkyl group and the alkyl group of said -Z(C_1-C_{15} alkyl) group being optionally substituted by C_1-C_{10} alkoxy, aryl, C_3-C_7 cycloalkyl or a group of the formula -Z(aryl), and the remainder of R^6, R^7 and R^8 and R^5 and R^9 are each independently selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, halo and halo(C_1-C_4 alkyl);

R^{10} is COOH, $COOR^{11}$ or $CONR^{12}R^{13}$;
R^{11} is a biolabile ester-forming group;
R^{12} and R^{13} are each independently selected from H and C_1-C_4 alkyl;
Z is O, $S(O)_q$, NH or N(C_1-C_6 alkyl);
q is 0, 1 or 2;
and "aryl", used in the definitions of X, R^6, R^7 and R^8, means phenyl optionally substituted by C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl, OH, halo, CF_3, halo(C_1-C_6 alkyl), nitro, amino, C_2-C_6 alkanamido, C_2-C_6 alkanoyl or phenyl.

Alkyl, haloalkyl, alkenyl and alkoxy groups containing three or more carbon atoms and alkanamido and alkanoyl groups containing four or more carbon atoms may be straight- or branched-chain.

The term "halo" means fluoro, chloro, bromo or iodo.

The term "biolabile ester-forming group" is well understood in medicinal chemistry as meaning a group which forms an ester which can be readily cleaved <u>in vivo</u> to liberate the corresponding acid of the formula (I) wherein R^{10} is COOH. A number of such ester groups are well-known, for example in the penicillin area or in the case of the angiotensin-converting enzyme (ACE) inhibitor antihypertensive agents.

Esters of the formula (I) wherein R^{10} is $-CO_2(C_1-C_6$ alkyl) are steroid 5α-reductase inhibitors per se but, in general, where R^{10} is $COOR^{11}$ such compounds are useful as pro-drugs to provide compounds of the formula (I) wherein R^{10} is COOH in vivo following oral administration. Such esters are also useful as intermediates for the preparation of compounds of the formula (I) wherein R^{10} is COOH.

The suitability of any particular ester-forming group for this purpose can be assessed by conventional in vitro or in vivo enzyme hydrolysis studies.

Examples of suitable biolabile ester-forming groups are alkyl (e.g. C_1-C_6 alkyl), alkanoyloxyalkyl(including alkyl, cycloalkyl or aryl substituted derivatives thereof), arylcarbonyloxyalkyl (including aryl substituted derivatives thereof), aryl, arylalkyl, indanyl and haloalkyl: wherein alkanoyl groups have from 2 to 8 carbon atoms and alkyl groups have from 1 to 8 carbon atoms, all of which may be straight- or branched-chain, and aryl means phenyl or naphthyl, both of which may be optionally substituted by C_1-C_4 alkyl, C_1-C_4 alkoxy or halo.

In addition to C_1-C_6 alkyl, specific examples of other biolabile ester-forming groups are benzyl, 1-(2,2-diethylbutyryloxy)ethyl, 2-ethylpropionyloxymethyl, 1-(2-ethylpropionyloxy)ethyl, 1-(2,4-dimethylbenzoyloxy)ethyl, α-benzoyloxybenzyl, 1-(benzoyloxy)ethyl, 2-methyl-1-propionyloxy-1-propyl, 2,4,6-trimethylbenzoyloxymethyl, 1-(2,4,6-trimethylbenzoyloxy)ethyl, pivaloyloxymethyl, phenethyl, phenpropyl, 2,2,2-trifluoroethyl, 1- or 2-naphthyl, 2,4-dimethylphenyl, 4-t-butylphenyl and 5-indanyl.

The pharmaceutically acceptable salts of the compounds of the formula (I) are the acid addition and the base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, benzoate, methanesulphonate, benzenesulphonate and p-toluenesulphonate salts.

Suitable base salts are formed from bases which form non-toxic salts and examples are the aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and diethanolamine salts.

For a review on suitable salts see Berge et al, J. Pharm. Sci., 66, 1-19 (1977).

In the above definitions relating to the present invention:

Preferably X is O, NH, C_1-C_4 alkylene or C_2-C_4 alkenylene.

More preferably X is O, NH, methylene, ethylene or ethenylene.

Most preferably X is methylene.

Preferably Y is C_1-C_6 alkylene.

Most preferably Y is propylene.

Preferably R is H or C_1-C_4 alkyl.

Most preferably R is H.

Preferably R^1, R^2, R^3 and R^4 are each H.

Preferably one of R^6, R^7 and R^8 is $-O(C_1-C_{15}$ alkyl), the alkyl of said $-O(C_1-C_{15}$ alkyl) group being optionally substituted by aryl, and the remainder of R^6, R^7 and R^8 and R^5 and R^9 are each H.

More preferably one of R^6, R^7 and R^8 is $-OCH_2$(aryl) or $-OCH(C_1-C_4$ alkyl)(aryl) and the remainder of R^6, R^7 and R^8 and R^5 and R^9 are each H.

Most preferably R^7 is $-OCH(CH_3)$(aryl) and R^5, R^6, R^8 and R^9 are each H.

Preferably R^{10} is COOH or $COOR^{11}$.
Most preferably R^{10} is COOH.

Preferably R^{11} is C_1-C_6 alkyl.
Most preferably R^{11} is ethyl.

Preferably Z is O.

Preferably "aryl" means phenyl optionally substituted by from 1 to 3 substituents, more preferably means phenyl optionally substituted by 1 or 2 substituents and most preferably means phenyl optionally substituted by one substituent.

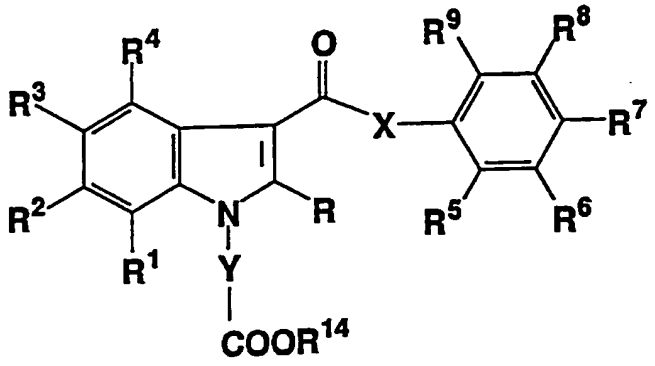
In a preferred aspect of the present invention "aryl" means phenyl optionally substituted by C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CF_3, nitro or phenyl and more preferably means phenyl optionally substituted by n-propyl, isobutyl, methoxy, chloro, CF_3, nitro or phenyl. Yet more preferably "aryl" means phenyl, 4-(n-propyl)phenyl, 4-isobutylphenyl, 4-methoxyphenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 4-trifluoromethylphenyl, 4-nitrophenyl or 4-phenylphenyl and most preferably means 4-isobutylphenyl.

A compound of the formula (I) may contain one or more asymmetric carbon atoms and/or one or more alkenyl groups and may therefore exist in two or more stereoisomeric forms. The present invention includes both the individual stereoisomers of the compounds of the formula (I) together with mixtures thereof. Separation of diastereoisomers or cis and trans isomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of the formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of the formula (I) may also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of a racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of a racemate with a suitable optically active acid or base.

Particularly preferred embodiments of the compounds of the formula (I) are
(R,S)-4-(3-[4-(1-[4-(2-methylpropyl)phenyl]ethoxy)-phenylethanoyl]indol-1-yl)butanoic acid and
(S)-4-(3-[4-(1-[4-(2-methylpropyl)phenyl]ethoxy)-phenylethanoyl]indol-1-yl)butanoic acid:
and the pharmaceutically acceptable salts thereof.

The compounds of formula (I) provided by the invention may be prepared by the following methods:-

1) The compounds of the formula (I) wherein R^{10} is COOH and X, Y, R and R^1 to R^9 are as previously defined for a compound of the formula (I) may be prepared by cleavage of an ester of the formula:-



....(II)

wherein R^{14} is a suitable ester-forming group and X, Y, R and R^1 to R^9 are as previously defined for a compound of the formula (I).

A plethora of suitable ester-forming groups that may be cleaved to provide the corresponding carboxylic acid are known to the skilled man, see, e.g., T.W. Greene and P.G. Wuts, "Protective Groups in Organic Synthesis", Wiley-Interscience (2nd edition, 1991).

Where R^{14} is an ester-forming group that may be removed by hydrolysis, e.g. C_1-C_6 alkyl or an alternative biolabile ester-forming group as previously defined (i.e. a compound of the formula (I) wherein R^{10} is $COOR^{11}$), the hydrolysis may be carried out under acidic or basic conditions, e.g. using an aqueous solution of either a suitable mineral acid or a suitable inorganic base. Preferably the hydrolysis is carried out under basic conditions.

In a typical procedure an ester of the formula (II) is treated with an aqueous solution of a suitable base, e.g. sodium or potassium hydroxide, and in the presence of a suitable organic co-solvent, e.g.

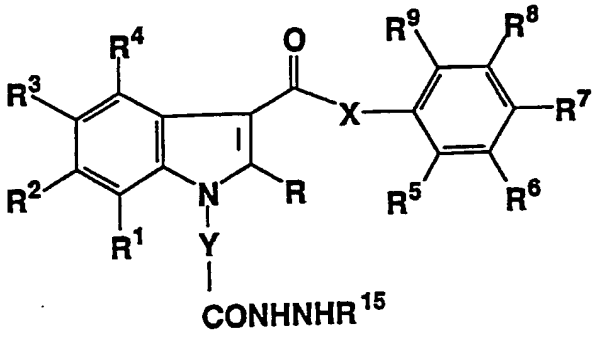
tetrahydrofuran or a C_1-C_4 alkanol such as methanol. The hydrolysis is typically carried out at from room temperature to the reflux temperature and preferably is carried out at room temperature. The product is obtained as a base salt which may be converted to the carboxylic acid by acidification in the work-up procedure.

Where R^{14} is an ester-forming group that may be removed by reduction, e.g. benzyl, the reduction may be carried out by catalytic hydrogenation using, e.g., palladium-on-charcoal, as the catalyst.

2) The compounds of the formula (I) wherein R^{10} is COOH and X, Y, R and R^1 to R^9 are as previously defined for a compound of the formula (I) may be prepared by hydrolysis of a compound of the formula (I) wherein R^{10} is $CONR^{12}R^{13}$ and X, Y, R, R^1 to R^9, R^{12} and R^{13} are as previously defined for a compound of the formula (I).

The hydrolysis may be carried out under acidic or basic conditions, e.g. using an aqueous solution of either a suitable mineral acid, e.g. hydrochloric or sulphuric acid, or a suitable inorganic base, e.g. sodium or potassium hydroxide, at from room temperature to the reflux temperature. When basic hydrolysis conditions are used the product is obtained as a base salt which may be converted to the carboxylic acid by acidification in the work-up procedure.

3) The compounds of the formula (I) wherein R^{10} is COOH and X, Y, R and R^1 to R^9 are as previously defined for a compound of the formula (I) may be prepared by hydrolysis of a compound of the formula:-

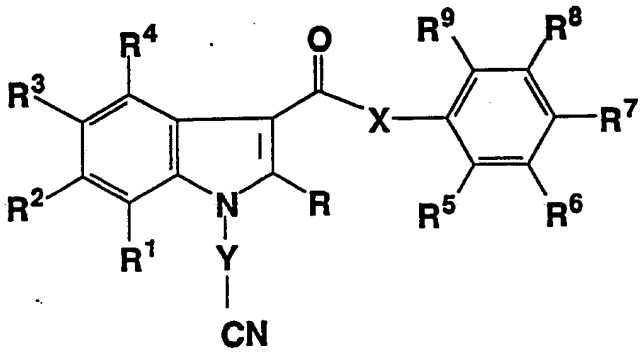


....(III)

wherein X, Y, R and R^1 to R^9 are as previously defined for a compound of the formula (I) and R^{15} is H or C_1-C_4 alkyl.

The hydrolysis may be carried out under acidic or basic conditions, e.g. using an aqueous solution of either a suitable acid, e.g. hydrochloric or acetic acid, or a suitable inorganic base, e.g. sodium or potassium hydroxide, at from room temperature to the reflux temperature. When basic hydrolysis conditions are used the product is obtained as a base salt which may be converted to the carboxylic acid by acidification in the work-up procedure.

4) The compounds of the formula (I) wherein R^{10} is COOH and X, Y, R and R^1 to R^9 are as previously defined for a compound of the formula (I) may be prepared by hydrolysis of a compound of the formula:-

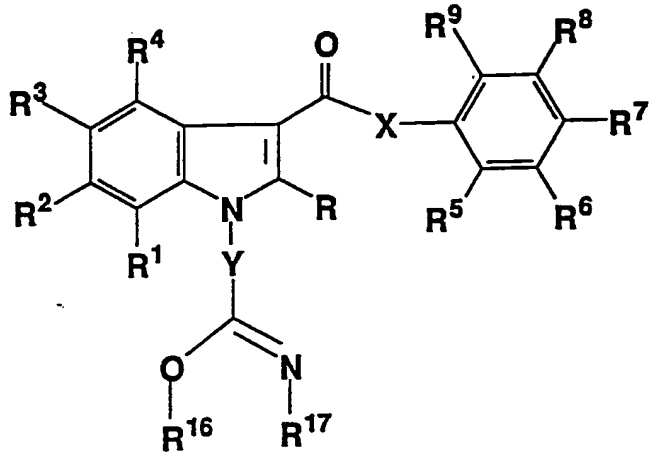


....(IV)

wherein X, Y, R and R^1 to R^9 are as previously defined for a compound of the formula (I).

The hydrolysis may be carried out under acidic or basic conditions, e.g. using an aqueous solution of either a suitable acid, e.g. hydrochloric or sulphuric acid, or a suitable inorganic base, e.g. sodium or potassium hydroxide, at from room temperature to the reflux temperature. When basic conditions are used hydrogen peroxide may optionally be present and also the product is obtained as a base salt which may be converted to the carboxylic acid by acidification in the work-up procedure.

5) The compounds of the formula (I) wherein R^{10} is COOH and X, Y, R and R^1 to R^9 are as previously defined for a compound of the formula (I) may be prepared by acidic hydrolysis of a compound of the formula:-



....(V)

wherein X, Y, R and R^1 to R^9 are as previously defined for a compound of the formula (I) and R^{16} and R^{17} taken together represent ethylene, said ethylene group being optionally substituted by phenyl or C_1-C_4 alkyl (preferably methyl). Preferably R^{16} and R^{17} taken together represent $-CH_2C(CH_3)_2-$.

The hydrolysis may be carried out using an aqueous solution of a suitable acid such as hydrochloric acid at from room temperature to the reflux temperature.

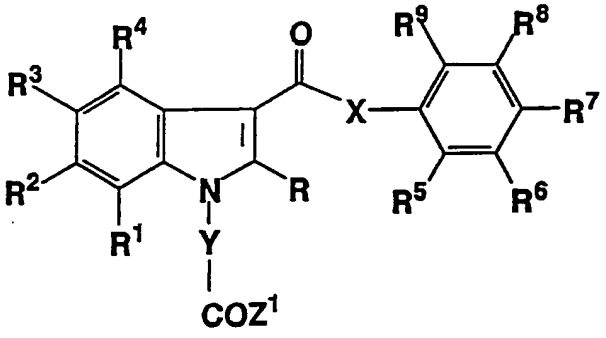
6) The compounds of the formula (I) wherein R^{10} is $CONH_2$ and X, Y, R and R^1 to R^9 are as previously defined for a compound of the formula (I) may be prepared by partial hydrolysis of a compound of the formula (IV) wherein X, Y, R and R^1 to R^9 are as previously defined for a compound of the formula (I). The hydrolysis may be carried out using concentrated sulphuric acid at from 0°C to room temperature.

7) The compounds of the formula (I) wherein R^{10} is $COOR^{11}$ and X, Y, R, R^1 to R^9 and R^{11} are as previously defined for a compound of the formula (I) may be prepared by esterification of a compound of the formula (I) wherein R^{10} is COOH and X, Y, R and R^1 to R^9 are as previously defined for a compound of the formula (I) with an alcohol of the formula $R^{11}OH$ wherein R^{11} is as previously defined for this method.

The reaction may be carried out under classical esterification conditions such as by using an excess of the alcohol and with acid catalysis, e.g. by sulphuric acid or p-toluenesulphonic acid, at from room temperature to the reflux temperature. The water generated during the reaction may be removed by azeotropic distillation or by the use of a dehydrating agent or a molecular sieve.
The esterification may also be carried out by reacting the acid with the alcohol in the presence of a dehydrating agent, e.g. dicyclohexylcarbodiimide or diethylazodicarboxylate/ triphenylphosphine (see O. Mitsunobu, Synthesis, 1981, 1).

Alternatively the esterification may be carried out by first forming an activated ester or imidazolide derivative of the carboxylic acid, followed by reaction of the activated ester or imidazolide <u>in situ</u> with the alcohol of the formula $R^{11}OH$. An activated ester may be formed by reacting the carboxylic acid with 1-hydroxybenzotriazole in the presence of a suitable dehydrating agent, e.g. 1-(3-N,N-dimethylaminopropyl)-3-ethylcarbodiimide, and in a suitable solvent, e.g. dichloromethane, at room temperature. An imidazolide may be formed by reacting the carboxylic acid with 1,1'-carbonyldiimidazole in a suitable solvent, e.g. dichloromethane, at room temperature.

8) The compounds of the formula (I) wherein R^{10} is $COOR^{11}$ wherein X, Y, R, R^1 to R^9 and R^{11} are as previously defined for a compound of the formula (I) may be prepared by reaction of a compound of the formula:-



....(VI)

wherein X, Y, R and R^1 to R^9 are as previously defined for a compound of the formula (I) and Z^1 is a suitable leaving group, e.g. chloro or bromo, with an alcohol of the formula $R^{11}OH$ wherein R^{11} is as previously defined for this method.

The reaction may be carried out in the presence of an acid acceptor, e.g. pyridine, and in a suitable solvent, e.g. dichloromethane, at from 0°C to room temperature.

9) The compounds of the formula (I) wherein R^{10} is $COOR^{11}$ wherein X, Y, R, R^1 to R^9 and R^{11} are as previously defined for a compound of the formula (I) may be prepared by reaction of a base salt of a compound of the formula (I) wherein R^{10} is COOH and X, Y, R and R^1 to R^9 are as previously defined for a compound of the formula (I) (i.e. a carboxylate base salt) with a compound of the formula $R^{11}Z^2$ wherein R^{11} is as previously defined for a compound of the formula (I) and Z^2 is a suitable leaving group, e.g. halo, preferably bromo or iodo, or p-toluenesulphonyloxy. Preferred base salts of the compounds of the formula (I) for use in this method are the sodium and potassium salts. The reaction may be carried out in a suitable solvent, e.g. dimethylformamide or tetrahydrofuran, at from room temperature to the reflux temperature.

10) The compounds of the formula (I) wherein R^{10} is $CONR^{12}R^{13}$ and X, Y, R, R^1 to R^9, R^{12} and R^{13} are as previously defined for a compound of the formula (I) may be prepared by reaction of a compound of the formula (I) wherein R^{10} is COOH and X, Y, R and R^1 to

R^9 are as previously defined for a compound of the formula (I), with an amine of the formula $R^{12}R^{13}NH$ wherein R^{12} and R^{13} are as previously defined for this method, in the presence of a dehydrating agent, e.g. dicyclohexylcarbodiimide. The reaction may be carried out in a suitable organic solvent, e.g. dichloromethane, at from room temperature to the reflux temperature.

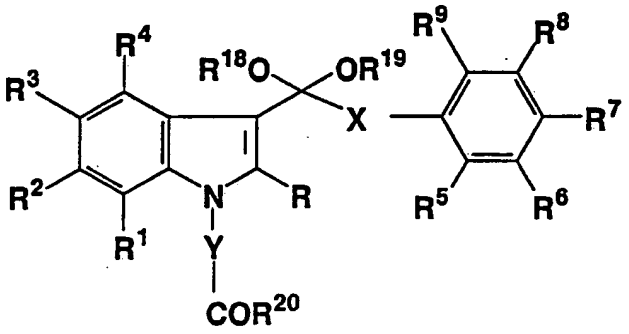
Alternatively the reaction may be carried out by first forming an activated ester or imidazolide derivative of the carboxylic acid, followed by reaction of the activated ester or imidazolide in situ with the amine of the formula $R^{12}R^{13}NH$. Suitable procedures for the formation of an activated ester or imidazolide are described in method (7).

11) The compounds of the formula (I) wherein R^{10} is $CONR^{12}R^{13}$ and X, Y, R, R^1 to R^9, R^{12} and R^{13} are as previously defined for a compound of the formula (I) may be prepared by reaction of a compound of the formula (VI) wherein X, Y, R, R^1 to R^9 and Z^1 are as previously defined for a compound of the formula (VI), with an amine of the formula $R^{12}R^{13}NH$ wherein R^{12} and R^{13} are as previously defined for this method. The reaction may be carried out in the presence of an acid acceptor, e.g. pyridine, and in a suitable solvent, e.g. dichloromethane, at from 0°C to room temperature.

12) The compounds of the formula (I) wherein R^{10} is $CONR^{12}R^{13}$ and X, Y, R, R^1 to R^9, R^{12} and R^{13} are as previously defined for a compound of the formula (I) may be prepared by reaction of a compound of the

formula (II) wherein R^{14} is a suitable ester-forming group, e.g. C_1-C_6 alkyl or an alternative biolabile ester-forming group as previously defined (i.e. a compound of the formula (I) wherein R^{10} is $COOR^{11}$), or p-nitrophenyl, and X, Y, R and R^1 to R^9 are as previously defined for a compound of the formula (I), with an amine of the formula $R^{12}R^{13}NH$ wherein R^{12} and R^{13} are as previously defined for this method. The reaction may be carried out in a suitable solvent, e.g. a C_1-C_4 alkanol, at from room temperature to the reflux temperature. The reaction is usually carried using an excess of the amine and in a sealed reaction vessel.

13) The compounds of the formula (I) wherein R^{10} is COOH or $CONR^{12}R^{13}$, X is C_1-C_4 alkylene, C_2-C_4 alkenylene or C_2-C_4 alkynylene, said alkylene, alkenylene and alkynylene groups being optionally substituted by C_1-C_4 alkyl or aryl, and Y, R, R^1 to R^9, R^{12} and R^{13} are as previously defined for a compound of the formula (I), may be prepared by acidic hydrolysis of a compound of the formula:-

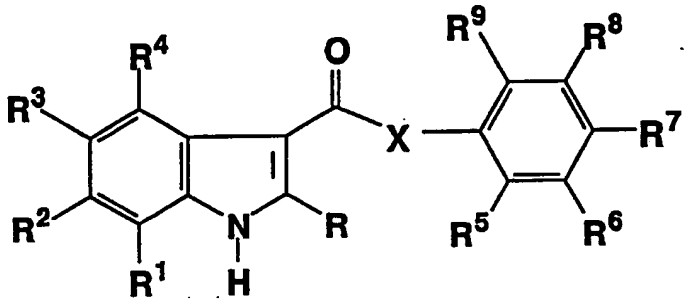


....(VII)

wherein X, Y, R and R^1 to R^9 are as previously defined for this method, R^{18} and R^{19} are either each C_1-C_4 alkyl or when taken together represent C_2-C_3 alkylene, said alkylene group being optionally substituted by C_1-C_4 alkyl, and R^{20} is OH, OR^{21} wherein R^{21} is a suitable ester-forming group that may be removed by hydrolysis, e.g. C_1-C_6 alkyl or an alternative biolabile ester-forming group as previously defined, or $NR^{12}R^{13}$ wherein R^{12} and R^{13} are as previously defined for this method. The hydrolysis may be carried out using a suitable acid, e.g. hydrochloric acid or p-toluenesulphonic acid, in the presence of water.

A compound of the formula (VII) may be prepared by first forming the corresponding ketal of a compound of the formula (VIII) wherein X, R and R^1 to R^9 are as previously defined for this method by reacting with the corresponding alcohol under acidic conditions, e.g. see T.W. Greene, "Protective Groups in Organic Synthesis", Wiley-Interscience (1981), followed by N-alkylation of the ketal by a similar procedure to that described in method (14) for alkylation of compounds of the formula (VIII).

14) All the compounds of the formula (I) wherein X, Y, R and R^1 to R^{10} are as previously defined for a compound of the formula (I) may be prepared by alkylation of a base salt (i.e. the N-deprotonated form) of a compound of the formula:-



....(VIII)

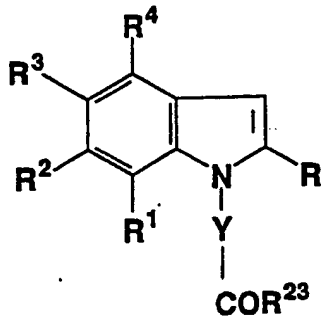
wherein X, R and R^1 to R^9 are as previously defined for a compound of the formula (I), with a compound of the formula Z^3-Y-$COOR^{22}$, Z^3-Y-$CONR^{12}R^{13}$ or a base salt of a compound of the formula Z^3-Y-COOH, as appropriate, wherein Y, R^{12} and R^{13} are as previously defined for a compound of the formula (I), Z^3 is a leaving group, e.g. halo, preferably chloro, bromo or iodo, methanesulphonyloxy or p-toluenesulphonyloxy, and R^{22} is a biolabile ester-forming group as previously defined for R^{11}. The preferred base salts of the compounds of the formula Z^3-Y-COOH are the alkali metal and alkaline earth metal salts, e.g. the sodium and potassium salts. The preferred base salts of the compounds of the formula (VIII) are the alkali metal salts, e.g. the sodium and potassium salts.

The reaction may be performed by initial deprotonation of the compound of the formula (VIII) with a suitable base, e.g. sodium hydride, followed by reaction of the resulting anion with the compound of the formula Z^3-Y-$COOR^{22}$, Z^3-Y-$CONR^{12}R^{13}$ or a base salt of the compound of the formula Z^3-Y-COOH, as required. The reaction may be carried out in a suitable solvent, e.g. N,N-dimethylformamide or tetrahydrofuran, at from 0°C to the reflux temperature and preferably at about room temperature. The reaction may also be carried out using potassium carbonate as the base and in 2-butanone as the solvent at about the reflux temperature of the solvent.

Alternatively the reaction may be carried out under phase transfer conditions where a suitable base is sodium or potassium hydroxide.

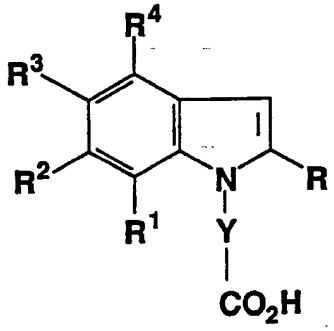
Where a compound of the formula (I) wherein R^{10} is COOH is required the product is obtained as a base salt which may be converted to the carboxylic acid by acidification in the work-up procedure.

15) The compounds of the formula (I) wherein X is C_1-C_4 alkylene, C_2-C_4 alkenylene or C_2-C_4 alkynylene, said alkylene, alkenylene and alkynylene groups being optionally substituted by C_1-C_4 alkyl or aryl, and Y, R and R^1 to R^{10} are as previously defined for a compound of the formula (I), may be prepared by acylation of an indole of the formula:-



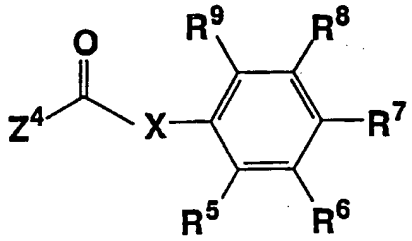
....(IX)

or, where R is OH, a base salt thereof,
or of a base salt of an indole of the formula:-



....(X)

wherein Y, R and R^1 to R^4 are as previously defined for a compound of the formula (I) and R^{23} is either OR^{24} wherein R^{24} is a biolabile ester-forming group as previously defined for R^{11}, or is $NR^{12}R^{13}$ wherein R^{12} and R^{13} are as previously defined for a compound of the formula (I), with a compound of the formula:-



....(XI)

wherein X and R^5 to R^9 are as previously defined for this method and Z^4 is a leaving group, e.g. halo, preferably chloro, and in the presence of a Lewis acid where R is not OH and optionally in the presence of a Lewis acid where R is OH. Suitable Lewis acids include aluminium chloride and diethylaluminium chloride.

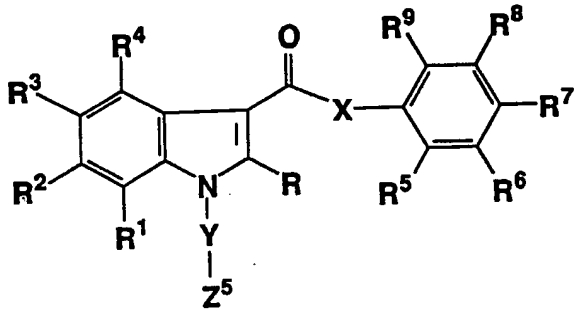
The reaction may be carried out in a suitable solvent, e.g. toluene, at from room temperature to the reflux temperature.

The preferred base salts of the indoles of the formula (X) are the alkali metal and alkaline earth metal salts, e.g. the sodium and potassium salts.

Where a compound of the formula (I) wherein R^{10} is COOH is required the product is obtained as a base salt which may be converted to the carboxylic acid by acidification in the work-up procedure.

Where a compound of the formula (I) wherein R is OH is required the compounds of the formulae (IX) and (X) must be in the form of an enolate salt. Accordingly an indole of the formula (IX) where R is OH or a base salt of an indole of the formula (X) where R is OH should first be treated with one equivalent of a suitable base, e.g. calcium hydroxide, to form an enolate salt which may then be acylated with a compound of the formula (XI), optionally in the presence of a Lewis acid. Incorporation of an acidification step in the work-up procedure affords the compound of the formula (I) wherein R is OH.

16) The compounds of the formula (I) wherein R^{10} is COOH, X is O, NH, N(C_1-C_4 alkyl) or C_1-C_4 alkylene, said alkylene group being optionally substituted by C_1-C_4 alkyl or aryl, and Y, R and R^1 to R^9 are as previously defined for a compound of the formula (I), may be prepared by oxidative cleavage of a compound of the formula:-

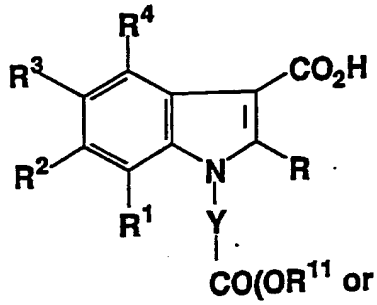


....(XII)

wherein Z^5 is $-CH=CH_2$, $-CH=CH(C_1-C_4$ alkyl), $-CH=C(C_1-C_4$ alkyl)$_2$ or $-C\equiv CH$ and X, Y, R and R^1 to R^9 are as previously defined for this method.

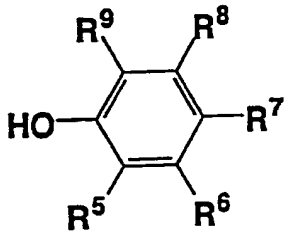
The reaction may be carried out by ozonolysis or by treatment with aqueous potassium permanganate solution.

17) The compounds of the formula (I) wherein X is O, R^{10} is either $COOR^{11}$ or $CONR^{12}R^{13}$ and Y, R, R^1 to R^9, R^{11}, R^{12} and R^{13} are as previously defined for a compound of the formula (I), may be prepared by esterification of a compound of the formula:-



....(XIII)

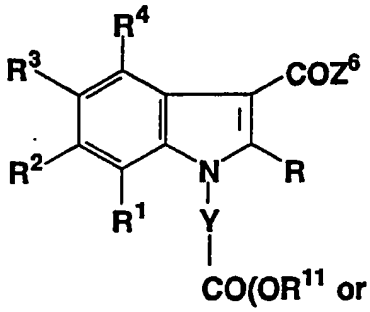
wherein Y, R, R^1 to R^4, R^{11}, R^{12} and R^{13} are as previously defined for this method, with a phenol of the formula:-



....(XIV)

wherein R^5 to R^9 are as previously defined for this method. A similar esterification procedure to any one of those described in method (7) may be used.

18) The compounds of the formula (I) wherein X, Y, R and R^1 to R^{10} are as defined for a compound of the formula (I) in method (17) may be prepared by reaction of a compound of the formula:-

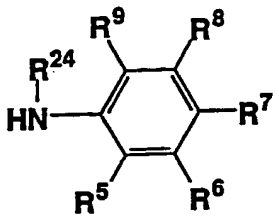


....(XV)

wherein Y, R, R^1 to R^4, R^{11}, R^{12} and R^{13} are as previously defined for this method and Z^6 is a leaving group, e.g. chloro or bromo, with a phenol of the formula (XIV) wherein R^5 to R^9 are as previously defined for this method.

The reaction may be carried out in the presence of an acid acceptor, e.g. pyridine, and in a suitable solvent, e.g. dichloromethane, at from 0°C to room temperature.

19) The compounds of the formula (I) wherein X is NH or N(C_1-C_4 alkyl), R^{10} is either $COOR^{11}$ or $CONR^{12}R^{13}$ and Y, R, R^1 to R^9, R^{11}, R^{12} and R^{13} are as previously defined for a compound of the formula (I), may be prepared by reaction of a compound of the formula (XIII) or an activated ester or imidazolide thereof, wherein Y, R, R^1 to R^4, R^{11}, R^{12} and R^{13} are as previously defined for this method, with an amine of the formula:-



....(XVI)

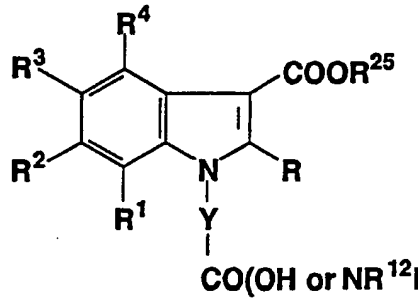
wherein R^{24} is H or C_1-C_4 alkyl and R^5 to R^9 are as previously defined for this method.

The reaction may be carried out in the presence of a suitable dehydrating agent, e.g. dicyclohexylcarbodiimide, and in a suitable organic solvent, e.g. dichloromethane, at from room temperature to the reflux temperature.

Alternatively the reaction may be carried out by first forming an activated ester or imidazolide derivative of the carboxylic acid, followed by reaction of the activated ester or imidazolide in situ with the amine. Suitable procedures for the formation of an activated ester or imidazolide are described in method (7).

20) The compounds of the formula (I) wherein X, Y, R and R^1 to R^{10} are as defined for a compound of the formula (I) in method (19) may be prepared by reaction of a compound of the formula (XV) wherein Y, R, R^1 to R^4, R^{11}, R^{12} and R^{13} are as previously defined for this method and Z^6 is as previously defined for a compound of the formula (XV), with an amine of the formula (XVI) wherein R^5 to R^9 and R^{24} are as previously defined for an amine of the formula (XVI). The reaction may be carried out in the presence of an acid acceptor, e.g. pyridine, and in a suitable solvent, e.g. dichloromethane, at from 0°C to room temperature.

21) The compounds of the formula (I) wherein X is NH or $N(C_1-C_4$ alkyl), R^{10} is COOH or $CONR^{12}R^{13}$ and Y, R, R^1 to R^9, R^{12} and R^{13} are as defined for a compound of the formula (I), may be prepared by reaction of a compound of the formula:-



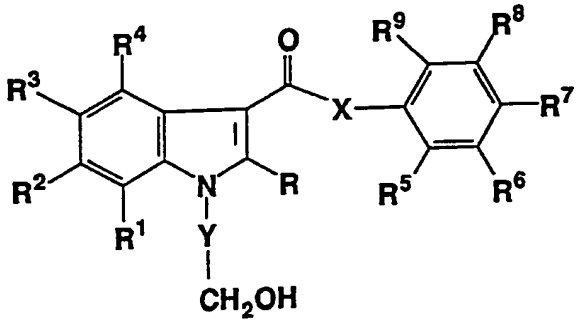
....(XVII)

or a base salt thereof,

wherein Y, R, R^1 to R^4, R^{12} and R^{13} are as previously defined for this method and R^{25} is a suitable ester-forming group, e.g. C_1-C_4 alkyl or p-nitrophenyl, with an amine of the formula (XVI) wherein R^5 to R^9 are as previously defined for this method and R^{24} is as previously defined for a compound of the formula (XVI).

The reaction may be carried out in a suitable solvent, e.g. a C_1-C_4 alkanol, at from room temperature to the reflux temperature.

22) The compounds of the formula (I) wherein R^{10} is COOH and X, Y, R and R^1 to R^9 are as previously defined for a compound of the formula (I), may be prepared by oxidation of a compound of the formula:-



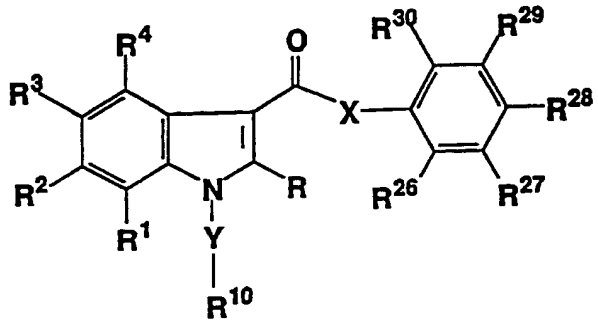
....(XVIII)

wherein X, Y, R and R^1 to R^9 are as previously defined for a compound of the formula (I). A suitable oxidising agent for this purpose is chromium trioxide in pyridine.

23) The compounds of the formula (I) wherein X is C_2-C_4 alkylene optionally substituted by C_1-C_4 alkyl or aryl, and Y, R and R^1 to R^{10} are as previously defined for a compound of the formula (I), may be prepared by reduction of a compound of the formula (I) wherein X is C_2-C_4 alkenylene or C_2-C_4 alkynylene, said alkenylene or alkynylene group being optionally substituted by C_1-C_4 alkyl or aryl, and Y, R and R^1 to R^{10} are as previously defined for a compound of the formula (I).

The reduction may be carried out using hydrogen in the presence of a suitable catalyst, e.g. palladium-on-charcoal, and in a suitable solvent, e.g. ethanol or ethyl acetate, at from room temperature to the reflux temperature and at a pressure of from one to five atmospheres (1.01×10^5 to 5.07×10^5 Pa).

24) The compounds of the formula (I) wherein one of R^6, R^7 and R^8 is a group of the formula -Z(C_1-C_{15} alkyl) or -Z(C_3-C_7 cycloalkyl), the alkyl of said -Z(C_1-C_{15} alkyl) group being optionally substituted by C_1-C_{10} alkoxy, aryl, C_3-C_7 cycloalkyl or a group of the formula -Z(aryl), Z is O, S, NH or N(C_1-C_6 alkyl) and the remainder of R^6, R^7 and R^8, R^5, R^9, X, Y, R, R^1 to R^4, R^{10} and "aryl" are as previously defined for a compound of the formula (I), may be prepared by reaction of a compound of the formula:-



....(XIX)

or a base salt thereof,

wherein one of R^{27}, R^{28} and R^{29} is a group of the formula $-Z^7-H$ wherein Z^7 is O, S, NH or N(C_1-C_6 alkyl) and the remainder of R^{27}, R^{28} and R^{29} are as previously defined for this method for the remainder of R^6, R^7 and R^8, R^{26} and R^{30} are as previously defined for this method for R^5 and R^9 and X, Y, R, R^1 to R^4 and R^{10} are as previously defined for this method, with a compound of the formula $R^{31}Z^8$ wherein R^{31} is C_1-C_{15} alkyl or C_3-C_7 cycloalkyl, as appropriate, said alkyl group being optionally substituted by C_1-C_{10} alkoxy, aryl, C_3-C_7 cycloalkyl or a group of the formula -Z(aryl), wherein "aryl" and Z are as previously defined for this method, and Z^8 is a suitable leaving group, e.g. halo, preferably chloro, bromo or iodo, methanesulphonyloxy or p-toluenesulphonyloxy.

The preferred base salts of the compounds of the formula (XIX) are the sodium and potassium salts.

Where Z^7 is O or S the reaction is preferably carried out using a base salt (i.e. a phenoxide or thiophenoxide base salt) of a compound of the formula (XIX) which may be generated <u>in situ</u> from the corresponding phenol or thiophenol of the formula (XIX) using a suitable base, e.g. sodium or potassium hydroxide or sodium hydride, and in a suitable solvent, e.g. ethanol or N,N-dimethylformamide, at from 0°C to the reflux temperature.

Where Z^7 is NH or N(C_1-C_6 alkyl) a compound of the formula (XIX) may be reacted with a compound of the formula $R^{31}Z^8$ in the presence of an additional acid acceptor, e.g. pyridine, and in a suitable organic solvent, e.g. dichloromethane.

25) The compounds of the formula (I) wherein R^{10} is $COOR^{11}$ or $CONR^{12}R^{13}$, one of R^6, R^7 and R^8 is a group of the formula -O(C_1-C_{15} alkyl), -O(aryl) or -O(C_3-C_7 cycloalkyl), the alkyl of said -O(C_1-C_{15} alkyl) group being optionally substituted by C_1-C_{10} alkoxy, aryl, C_3-C_7 cycloalkyl or a group of the formula -Z(aryl), and the remainder of R^6, R^7 and R^8, R^5, R^9, X, Y, Z, R, R^1 to R^4, R^{11}, R^{12}, R^{13} and "aryl" are as previously defined for a compound of the formula (I), may be prepared by reaction of a compound of the formula (XIX) wherein one of R^{27}, R^{28} and R^{29} is OH and the remainder of R^{27}, R^{28} and R^{29} and R^{26} and R^{30} are as previously defined for a compound of the formula (XIX) in method (24) and X, Y, R, R^1 to R^4 and R^{10} are as previously defined for this method, with a compound of the formula $R^{32}OH$ wherein R^{32} is C_1-C_{15} alkyl, aryl or C_3-C_7 cycloalkyl, as appropriate,

said alkyl group being optionally substituted by C_1-C_{10} alkoxy, aryl, C_3-C_7 cycloalkyl or a group of the formula -Z(aryl), wherein "aryl" and Z are as previously defined for this method, in the presence of a suitable dehydrating agent, e.g. diethylazodicarboxylate/triphenylphosphine. The reaction may be carried out in a suitable solvent, e.g. tetrahydrofuran, at from room temperature to the reflux temperature.

26) The compounds of the formula (I) wherein X is CH(C_1-C_4 alkyl), R^{10} is $COOR^{11}$ or $CONR^{12}R^{13}$ and Y, R, R^1 to R^9, R^{11}, R^{12} and R^{13} are as previously defined for a compound of the formula (I), may be prepared by alkylation of a base salt of a compound of the formula (I) wherein X is CH_2 and Y, R and R^1 to R^{13} are as previously defined for this method, with a compound of the formula (C_1-C_4 alkyl)Z^9 wherein Z^9 is a suitable leaving group, e.g. halo, preferably chloro, bromo or iodo, methanesulphonyloxy or p-toluenesulphonyloxy.

The preferred base salts of the compounds of the formula (I) for use in this method are the sodium and potassium salts.

The reaction may be carried out by first reacting a compound of the formula (I) wherein X is CH_2 with a suitable base, e.g. sodium hydride, and in a suitable solvent, e.g. N,N-dimethylformamide, at from 0°C to room temperature, followed by <u>in situ</u> alkylation of the base salt formed with a compound of the formula (C_1-C_4 alkyl)Z^9.

All of the above reactions and the preparations of novel starting materials used in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well known to those skilled in the art with reference to literature precedents and the Examples and Preparations hereto.

A pharmaceutically acceptable salt of a compound of the formula (I) may be readily prepared by mixing together solutions of a compound of the formula (I) and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or is recovered by evaporation of the solvent.

The compounds of the formula (I) are steroid 5α-reductase inhibitors and they are therefore useful in the curative or prophylactic treatment of diseases or conditions such as acne vulgaris, alopecia, seborrhoea, female hirsutism, benign prostatic hypertrophy and male pattern baldness. Certain compounds of the formula (I) are also useful in the treatment of human prostate adenocarcinomas.

The compounds of the formula (I) may be tested in vitro for steroid 5α-reductase inhibitory activity using prostate tissue from rats or humans.

The compounds of the formula (I) may be tested for potency in inhibiting rat steroid 5α-reductase using ventral prostate tissue from male rats. In determining inhibitory potency against rat prostatic 5α-reductase the following procedure was employed:-

Rat prostates were minced into small pieces. The tissue was homogenised in Buffer A (20mM sodium phosphate, pH 6.5, buffer containing 0.32M sucrose and 1mM dithiothreitol) with a Brinkman Polytron (Kinematica, Luzern, GmBH), and then homogenised with a motor driven (1000rpm) Potter Elvehjem (teflon-to-glass) homogeniser. Prostate particles were obtained by centrifugation at 105,000G for 60 minutes. The pellet was washed in 4 volumes of Buffer A and recentrifuged at 105,000G. The resulting pellet was dispersed in Buffer A (1ml per g of prostate tissue originally used) with a motor driven Potter Elvehjem homogeniser as described above. The particulate suspension was stored as 1ml samples at -70°C.

The following components, dissolved in Buffer B (40mM sodium phosphate buffer, pH 6.5), were added to a test tube: 500µl of [^{3}H]-testosterone (1µCi, 1nmol; Du Pont, NEN Research Products, Stevenage, U.K.), 100µl of 0.5mM NADPH, a compound of the formula (I) dissolved in 5µl of dimethyl sulphoxide, and Buffer B to give a final reaction volume of 1ml. The mixture was warmed to 37°C and the reaction started by addition of an aliquot of prostate particulate suspension. The reaction mixture was incubated at 37°C for 30 minutes and then quenched by addition with vigorous mixing of 2ml of ethyl acetate containing 20µg each of testosterone and 5α-dihydrotestosterone as carriers. The aqueous and organic layers were separated by centrifugation at 2000G for 10 minutes. The organic layer was transferred to a second test tube and evaporated to dryness under nitrogen. The residue was dissolved in 50-80µl of absolute ethanol and spotted onto a silica gel 60 F254 TLC plate (E. Merck, Darmstadt, Germany) and developed in chloroform:acetone (185:15).

The radiochemical content in the bands of the substrate (testosterone) and the product (5α-dihydrotestosterone) was determined with a RITA Radio TLC Analyser (Raytest Instruments Ltd., Sheffield, U.K.). The percent of recovered radiolabel converted to 5α-dihydrotestosterone was calculated and used to determine enzyme activity. All incubations were conducted so that no more than 15% of substrate (testosterone) was converted to product.

The experimentally obtained data for a range of inhibitor concentrations was computer fitted to a sigmoidal dose-response curve and concentrations of compound giving 50% inhibition of 5α-reductase activity (IC_{50}'s) were calculated using a SIGFIT program (De Lean, A., Munson, P.J. and Rodbard, D., American Journal of Physiology, 235, E97 (1978)).

The compounds of the formula (I) may be tested for potency in inhibiting human steroid 5α-reductase using tissue from hyperplastic human prostates. In determining inhibitory potency against human prostatic 5α-reductase the following procedure was employed:-

Frozen human prostate tissue was pulverised in liquid nitrogen using a steel mortar and pestle. The powdered tissue was homogenised in 4 volumes of Buffer A (20mM sodium phosphate, pH 6.5, containing 0.32M sucrose, 1mM dithiothreitol and 50μM NADPH) with an Ultra-Turrax (Janke and Kunkel GmBH & Co., Staufen i.BR., Germany). The homogenate was centrifuged at 500G for 5 minutes, to remove large particles of tissue, and the supernatant was then centrifuged at 100,000G for 1 hour. The resulting

pellet was dispersed in Buffer A (1ml per g of prostate tissue originally used) with the Ultra-Turrax homogeniser. This particulate preparation was then filtered through 2 layers of cheesecloth and the filtrate was stored as 1ml samples at -70°C.

The following components, dissolved in Buffer B (20mM citrate phosphate buffer, pH 5.2), were added to a test tube: 500µl of [^{3}H]-testosterone (1µCi, 1nmol; Du Pont, NEN Research Products, Stevenage, U.K.), 100µl of NADPH regeneration system (5mM NADPH, 50mM glucose 6-phosphate, 5 units/ml glucose 6-phosphate dehydrogenase), a compound of the formula (I) dissolved in 5µl of dimethyl sulphoxide, and Buffer B to give a final reaction volume of 1ml. The mixture was warmed to 37°C and the reaction started by addition of an aliquot of prostate particulate suspension. The reaction mixture was incubated at 37°C for 30 minutes and then quenched by addition with vigorous mixing of 2ml of ethyl acetate containing 20µg each of testosterone and 5α-dihydrotestosterone as carriers. The aqueous and organic layers were separated by centrifugation at 2000G for 10 minutes. The organic layer was transferred to a second test tube and evaporated to dryness under nitrogen. The residue was dissolved in 50-80µl of absolute ethanol and spotted onto a silica gel 60 F254 TLC plate (E. Merck, Darmstadt, Germany) and developed in chloroform:acetone (185:15).

The radiochemical content in the bands of the substrate (testosterone) and the product (5α-dihydrotestosterone) was determined with a RITA Radio TLC Analyser (Raytest Instruments Ltd., Sheffield, U.K.). The percent of recovered radiolabel converted to 5α-dihydrotestosterone was calculated and used to determine enzyme activity. All incubations were conducted so that no more than 15% of substrate (testosterone) was converted to product.

The experimentally obtained data for a range of inhibitor concentrations was computer fitted to a sigmoidal dose-response curve and concentrations of compound giving 50% inhibition of 5α-reductase activity (IC_{50}'s) were calculated using a SIGFIT program (De Lean, A., Munson, P.J. and Rodbard, D., American Journal of Physiology, 235, E97 (1978)).

The compounds of the formula (I) may be tested for potency in inhibiting steroid 5α-reductase activity in human prostate adenocarcinomas using cell lines DU145 and HPC36M. In determining inhibitory potency against 5α-reductase the following procedure was employed:-

Human prostate adenocarcinoma cell lines were grown in Dulbecco's Modified Eagles medium (DMEM) containing 5% serum. The cells were recovered from the medium by centrifugation, washed in serum free DMEM and suspended at 5-10 x 10^6 cells/ml. in serum free medium.

The following components were added to a test tube: 10μl of [^{3}H]-testosterone (1μCi, 20 pmol) dissolved in ethanol (Du Pont, NEN Research Products, Stevenage, U.K.) and 5μl of an ethanol solution of a compound of the formula (I). The ethanol was evaporated under nitrogen and the testosterone and the compound redissolved in 0.25ml of serum free medium containing 0.25μmol NADPH. The mixture was warmed to 37°C and the reaction started by addition of 0.25ml of cell suspension (1.2-2.5 x 10^6 cells). The reaction mixture was incubated at 37°C for 2 hours and then quenched by addition with vigorous mixing of 1.5ml of ethyl acetate containing 20μg each of testosterone and 5α-dihydrotestosterone as carriers. The aqueous and organic layers were separated by centrifugation at 2000G for 10 minutes. The organic layer, containing testosterone and its metabolites, was transferred to a second test tube and evaporated to dryness under nitrogen. The residue was dissolved in 50-80μl of absolute ethanol, spotted onto a silica gel 60 F254 TLC plate (E. Merck, Darmstadt, Germany) and developed in dichloromethane:acetone (185:15).

The radiochemical content in the bands of the substrate (testosterone) and the product (5α-dihydrotestosterone) was determined with a RITA Radio TLC Analyser (Raytest Instruments Ltd., Sheffield, U.K.). The percentage of recovered radiolabel converted to 5α-dihydrotestosterone was calculated and used to determine enzyme activity. All incubations were conducted so that no more than 15% of substrate (testosterone) was converted to product.

The experimentally obtained data for a range of inhibitor concentrations was computer fitted to a sigmoidal dose-response curve and concentrations of compound giving 50% inhibition of 5α-reductase activity (IC_{50}'s) were calculated using a SIGFIT program (De Lean, A., Munson, P.J. and Rodbard D., American Journal of Physiology, 235, E97 (1978)).

For human use, the compounds of the formula (I) can be administered alone but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they can be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs, solutions or suspensions containing flavouring or colouring agents. They can be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

For oral and parenteral administration to human patients the daily dosage level of the compounds of the formula (I) will be from 0.01 to 20 mg/kg (in single or divided doses) and preferably will be from 0.1 to 10mg/kg except for the treatment of human prostate adenocarcinomas where doses of up to 20mg/kg may be used. Thus tablets or capsules of the compounds will contain from 1mg to 0.5g of active compound for administration singly or two or more at a time, as appropriate. The physician in

any event will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention.

Alternatively, the compounds of the formula (I) can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. For example, they can be incorporated into a cream consisting of an aqueous emulsion of polyethylene glycols or liquid paraffin; or they can be incorporated, at a concentration between 1 and 10%, into an ointment consisting of a white wax or white soft paraffin base together with such stabilizers and preservatives as may be required.

The compounds of the formula (I) may also be administered together with an α-antagonist (e.g. prazosin or doxazosin), an antiandrogen (e.g. flutamide) or an aromatase inhibitor (e.g. atamestane), particularly for the curative or prophylactic treatment of benign prostatic hypertrophy.

Thus the invention further provides:-

i) a pharmaceutical composition comprising a compound of the formula (I), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier;

ii) a compound of the formula (I), or a pharmaceutically acceptable salt or composition thereof, for use as a medicament;

iii) the use of a compound of the formula (I), or of a pharmaceutically acceptable salt or composition thereof, for the manufacture of a medicament for inhibiting a steroid 5α-reductase;

iv) the use of a compound of the formula (I), or of a pharmaceutically acceptable salt or composition thereof, for the manufacture of a medicament for the curative or prophylactic treatment of acne vulgaris, alopecia, seborrhoea, female hirsutism, benign prostatic hypertrophy, male pattern baldness or a human prostate adenocarcinoma;

v) a method of treatment of a human to inhibit a steroid 5α-reductase which comprises treating said human with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt or composition thereof;

vi) a method of treatment of a human to cure or prevent acne vulgaris, alopecia, seborrhoea, female hirsutism, benign prostatic hypertrophy, male pattern baldness or a human prostate adenocarcinoma which comprises treating said human with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt or composition thereof; and

vii) novel intermediates of the formulae (II) (with the proviso that R^{14} is not as defined for R^{11}), (IV), (VIII) or a base salt thereof and (XIX) or a base salt thereof.

The following Examples illustrate the preparation of the compounds of the formula (I):-

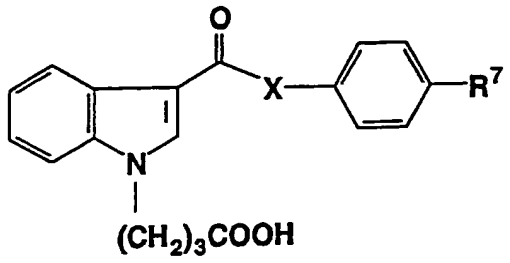
ILLUSTRATIVE METHOD 1

(R,S)-4-(3-[4-(1-[4-(2-Methylpropyl)phenyl]ethoxy)-benzoyl]indol-1-yl)butanoic acid

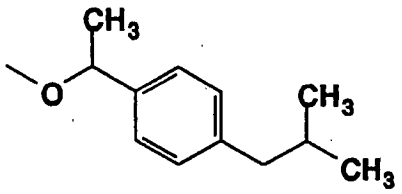
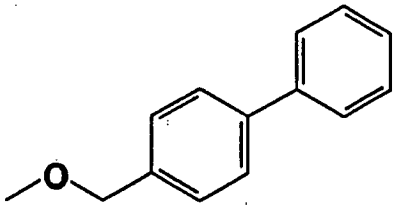
A solution of (R,S)-4-(3-[4-(1-[4-(2-methylpropyl)phenyl]ethoxy)benzoyl]indol-1-yl)butanoic acid ethyl ester (3.8g) in tetrahydrofuran(THF) (35ml) and methanol (35ml) was treated with 2N sodium hydroxide solution (35ml). After stirring at room temperature for 2 hours the mixture was cautiously concentrated in vacuo to a volume of about 50ml then cooled in an ice-bath and acidified with 2N hydrochloric acid solution. The acid phase was extracted with ethyl acetate (100ml), the organic extract dried (sodium sulphate) and concentrated in vacuo to provide the title compound as a white foam, (3.27g).

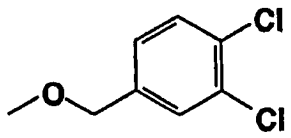
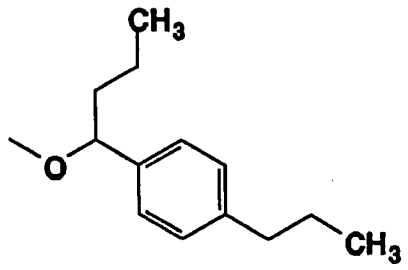
EXAMPLES 1 to 18

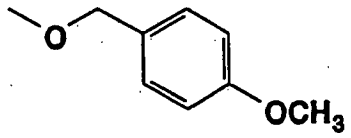
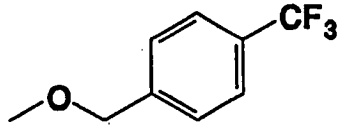
The following compounds of the general formula:-

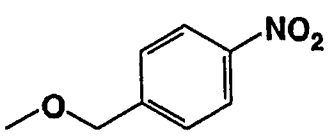
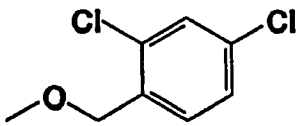


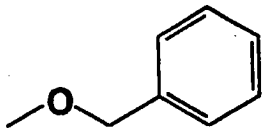
or base salts thereof, were prepared by hydrolysis of the corresponding ethyl esters (see Examples 19 to 36) by similar methods to that used in illustrative Method 1.

Example No.	X	R^7	m.p. (°C)	m/z	Analysis/NMR
1	CH_2		-	498 $(M+1)^+$	Found: C,76.18; H,6.82; N,2.62; $C_{32}H_{35}NO_4.½H_2O$ requires: C,75.86; H,7.16; N,2.76%. ^{1}H-NMR (d_6-DMSO): δ = 0.85 (d,6H), 1.45(d,3H), 1.75 (m,1H), 2.00(m,2H), 2.20 (t,2H), 2.35(d,2H), 3.95 (s,2H), 4.25(t,2H), 5.35 (q,1H), 6.75(d,2H), 7.05-7.30(m,8H), 7.55(d,1H), 8.10(d,1H), 8.50(s,1H) ppm.
2	CH_2		-	504 $(M+1)^+$	Found: C,77.58; H,6.35; N,2.46; $C_{33}H_{29}NO_4.¼CH_3CO_2C_2H_5$ requires: C,77.69; H,5.94; N,2.66%. ^{1}H-NMR (d_6-DMSO): δ = 2.20 (m,2H), 2.35(t,2H), 4.10 (s,2H), 4.25(t,2H), 5.05 (s,2H), 6.95(d,2H), 7.20-7.60(m,15H), 8.40(m,1H) ppm.

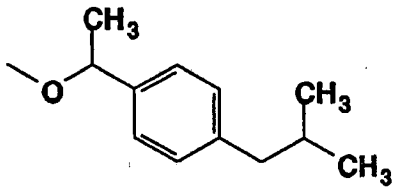
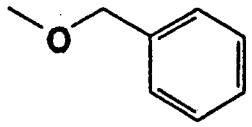
Example No.	X	R^7	m.p. (°C)	m/z	Analysis/NMR
3	CH_2		-	496 (M+)	Found: C,64.68; H,5.30; N,2.50; $C_{27}H_{23}Cl_2NO_4.½CH_3CO_2C_2H_5$ requires: C,64.45; H,5.04; N,2.59%. ^{1}H-NMR (d_6-DMSO): δ = 2.20 (m,2H), 2.35(t,2H), 4.10 (s,2H), 4.25(t,2H), 4.95 (s,2H), 6.90(d,2H), 7.20-7.50(m,8H), 7.75(s,1H), 8.40(m,1H) ppm.
4	CH_2		-	512 $(M+1)^+$	Found: C,78.11; H,7.23; N,2.99; $C_{33}H_{37}NO_4$ requires: C,77.47; H,7.29; N,2.74%. ^{1}H-NMR (d_6-DMSO): 0.90 (m,6H), 1.30-2.00(m,7H), 2.20(m,2H), 2.35(t,2H), 2.49(t,2H), 4.00(s,2H), 4.10(t,2H), 5.00(m,1H), 6.80(d,2H), 7.10-7.40 (m,9H), 7.75(s,1H), 8.40(m,1H) ppm.

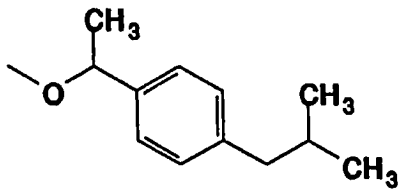
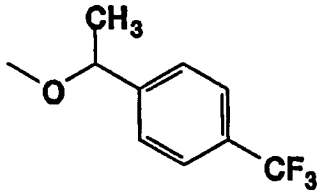
Example No.	X	R^7	m.p. (°C)	m/z	Analysis/NMR
5	CH_2		-	457 (M+)	^{1}H-NMR (d_6-DMSO): δ = 2.20 (m,2H), 2.35(t,2H), 3.80 (s,3H), 4.10(s,2H), 4.25 (t,2H), 4.95(s,2H), 6.90 (m,4H), 7.20-7.40(m,7H), 7.80(s,1H), 8.40(m,1H) ppm.
6	CH_2		-	496 $(M+1)^+$	Found: C,65.73; H,4.83; N,2.91; $C_{28}H_{24}F_3NO_4$.3/4 H_2O requires: C,66.07; H,5.05; N,2.75%. ^{1}H-NMR (d_6-DMSO): δ = 2.20 (m,2H), 2.40(t,2H), 4.05 (s,2H), 4.25(t,2H), 5.05 (s,2H), 6.90(d,2H), 7.25-7.60(m,9H), 7.80(s,1H), 8.40(m,1H) ppm.

Example No.	X	R^7	m.p. (°C)	m/z	Analysis/NMR
7	CH_2		-	473 $(M+1)^+$	Found: C,68.37; H,5.32; N,5.80; $C_{27}H_{24}N_2O_6$ requires: C,68.63; H,5.12; N,5.93%. ^{1}H-NMR (d_6-DMSO): δ = 2.20 (m,2H), 2.40(t,2H), 4.10 (s,2H), 4.25(t,2H), 5.15 (s,2H), 6.90(d,2H), 7.25-7.40(m,5H), 7.60(d,2H), 7.80(s,1H), 8.25(d,2H), 8.40(m,1H) ppm.
8	CH_2		-	-	Found: C,65.06; H,4.81; N,2.71; $C_{27}H_{23}Cl_2NO_4$ requires: C,65.33; H,4.67; N,2.82%. ^{1}H-NMR (d_6-DMSO): δ = 2.20 (m,2H), 2.40(t,2H), 4.10 (s,2H), 4.25(t,2H), 5.05 (s,2H), 6.95(d,2H), 7.20-7.50(m,9H), 7.90(s,1H), 8.40(m,1H) ppm.

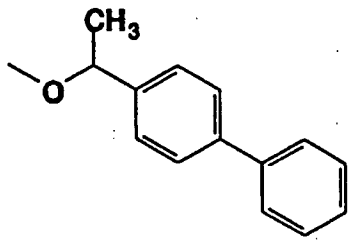
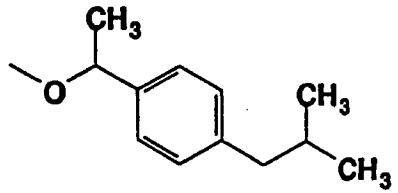
Example No.	X	R^7	m.p. (°C)	m/z	Analysis/NMR
9	CH_2		-	428 $(M+1)^+$	Found: C,74.76; H,5.84; N,3.17; $C_{27}H_{25}NO_4.½H_2O$ requires: C,74.30; H,6.00; N,3.21%. ^{1}H-NMR (d_6-DMSO): δ = 2.05 (m,2H), 2.25(t,2H), 4.05 (s,2H), 4.30(t,2H), 5.05 (s,2H), 6.95(d,2H), 7.20-7.40(m,7H), 7.60(d,1H), 8.20(d,1H), 8.60(s,1H) ppm.
10	CH_2	$-OCH(CH_2CH_2CH_3)_2$	-	436 (M+)	Found: C,69.95; H,7.51; N,2.76; $C_{27}H_{33}NO_4.1½H_2O$ requires: C,70.11; H,7.19; N,3.03%. ^{1}H-NMR ($CDCl_3$): δ = 0.90 (t,6H), 1.20-1.70(m,8H), 2.20(m,2H), 2.35(t,2H), 4.05(s,2H), 4.20(m,1H), 4.25(t,2H), 6.80(d,2H), 7.20-7.40(m,5H), 7.80(s,1H), 8.40(m,1H) ppm.

Example No.	X	R^7	m.p. (°C)	m/z	Analysis/NMR
11	NH		155-156	428 (M+)	Found: C,73.23; H,5.85; N,6.57; $C_{28}H_{24}N_2O_4$ requires: C,72.88; H,5.65; N,6.54%. ^{1}H-NMR (d_6-DMSO): δ = 2.15 (m,2H), 2.25(t,2H), 4.20 (t,2H), 5.00(s,2H), 6.90 (d,2H), 7.20-7.40(m,8H), 7.50(d,2H), 7.80(s,1H), 8.10(m,2H) ppm.
12	O		186-187	430 (M+)	Found: C,72.38; H,5.38; N,3.29; $C_{28}H_{24}NO_6$ requires: C,72.54; H,5.62; N,3.25%. ^{1}H-NMR (d_6-DMSO): δ = 2.15 (m,2H), 2.25(t,2H), 4.20 (t,2H), 5.00(s,2H), 6.90 (d,2H), 7.10(d,2H), 7.20-7.40(m,8H), 7.95(s,1H), 8.10(m,1H) ppm.

Example No.	X	R^7	m.p. (°C)	m/z	Analysis/NMR
13	NH		166-167	499 (M+)	Found: C,74.11; H,6.62; N,5.61; $C_{31}H_{34}N_2O_4$ requires: C,74.67; H,6.87; N,5.62%. ^{1}H-NMR (d_6-DMSO): δ = 0.80 (d,6H), 1.55(d,3H), 1.75 (m,1H), 2.10(m,2H), 2.20 (t,2H), 2.40(d,2H), 4.15 (t,2H), 5.20(q,1H), 6.80 (d,2H), 7.05(d,2H), 7.20-7.40(m,7H), 7.75(s,1H), 8.05(m,1H), 8.15(s,br,1H) ppm.
14	CH=CH (trans)		135-136	439 (M+)	Found: C,76.07; H,5.60; N,3.18; $C_{28}H_{25}NO_4$ requires: C,76.52; H,5.73; N,3.19%. ^{1}H-NMR (d_6-DMSO): δ = 2.10(m,2H), 2.26(m,2H), 4.30(m,2H), 5.20(s,2H), 7.12(d,2H), 7.20-7.78 (m,10H), 7.84(d,2H), 8.35 (d,1H), 8.78(s,1H) ppm.

Example No.	X	R^7	m.p. (°C)	m/z	Analysis/NMR
15[1]	$(CH_2)_2$		-	534 $(M+1)^+$	Found: C,73.85; H,7.04; N,2.53; $C_{33}H_{36}NaNO_4$ requires: C,74.28; H,6.80; N,2.62%. ^{1}H-NMR (d_6-DMSO): δ = 0.80 (d,6H), 1.44(d,3H), 1.65 (septet,1H), 1.94(m,2H), 2.12(t,2H), 2.35(d,2H), 2.80(t,2H), 3.06(t,2H), 4.18(t,2H), 5.35(q,1H), 6.75(d,2H), 7.00-7.30 (m,8H), 7.52(d,1H), 8.12(d,1H), 8.35(s,1H) ppm.
16	CH_2		-	510 $(M+1)^+$	Found: C,67.00; H,5.24; N,2.54; $C_{29}H_{26}F_3NO_4.½H_2O$ requires: C,67.17; H,5.05; N,2.70%. ^{1}H-NMR ($CDCl_3$): δ = 1.60(d,3H), 2.20(m,2H), 2.38(m,2H), 4.02(s,2H), 4.24(t,2H), 5.25(q,1H), 6.75(d,2H), 7.15(d,2H), 7.28-7.40(m,3H), 7.45(d,2H), 7.58(d,2H), 7.77(s,1H), 8.40(m,1H) ppm.

[1] Isolated as the sodium salt.

Example No.	X	R^7	m.p. (°C)	m/z	Analysis/NMR
17	CH_2		-	517 (M^+)	Found: C,76.71; H,6.16; N,2.60; $C_{34}H_{31}NO_4.3/4H_2O$ requires: C,76.89; H,5.88; N,2.64%. ^{1}H-NMR ($CDCl_3$): δ = 1.65(d,3H), 2.20(m,2H), 2.35(t,2H), 4.00(s,2H), 4.20(t,2H), 5.30(q,1H), 6.80(d,2H), 7.18(d,2H), 7.20-7.58(m,12H), 7.70(s,1H), 8.40(m,1H) ppm.
18	$CH(CH_3)$		-	511 (M^+)	Found: C,76.26; H,7.22; N,2.64; $C_{33}H_{37}NO_4.½H_2O$ requires: C,76.13; H,7.16; N,2.69%. ^{1}H-NMR ($CDCl_3$): δ = 0.85(d,6H), 1.50(d,3H), 1.55(d,3H), 1.80(m,1H), 2.15(m,2H), 2.25(m,2H), 2.40(m,2H), 4.20(m,2H), 4.32(q,1H), 5.21(q,2H), 6.78(d,2H), 7.05(m,2H), 7.15-7.35 (m,6H), 7.60(m,1H), 8.40(m,1H) ppm.

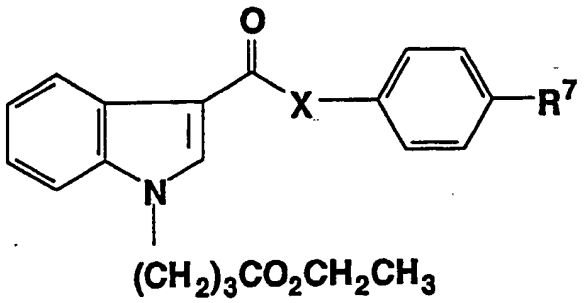
ILLUSTRATIVE METHOD 2

(R,S)-4-(3-[4-(1-[4-(2-Methylpropyl)phenyl]-ethoxy)benzoyl]indol-1-yl)butanoic acid ethyl ester

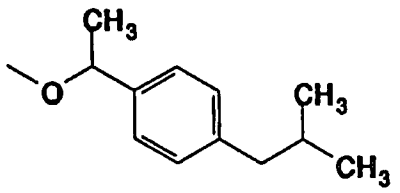
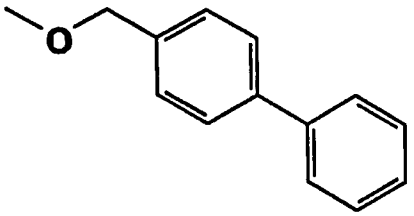
A suspension of sodium hydride (60% dispersion in oil, 716mg) in dry dimethylformamide(DMF) (15ml) at 0°C and under a nitrogen atmosphere was treated dropwise with a solution of 4-(3-[4-hydroxybenzoyl]indol-1-yl)butanoic acid ethyl ester (5.24g) in dimethylformamide (30ml). After stirring for one hour at room temperature a solution of α-methyl-4-(2-methylpropyl)benzyl bromide (3.95g) in dimethylformamide (5ml) was added to the mixture at 0°C. The resultant mixture was stirred overnight at room temperature. The reaction was partitioned between 1N hydrochloric acid solution (100ml) and ethyl acetate (200ml). The separated organic layer was washed successively with 1N sodium hydroxide solution (100ml), saturated aqueous brine (100ml) and then water (100ml). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to provide a yellow oil. Column chromatography (silica, 4.1 hexane/ethyl acetate) provided, after evaporation of the appropriate fractions, the title compound, (3.8g).

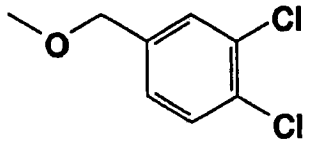
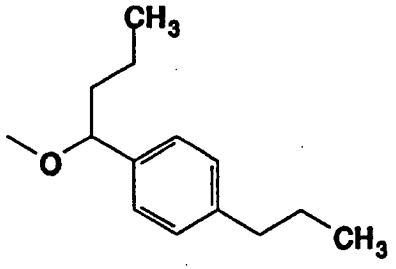
EXAMPLES 19 to 30

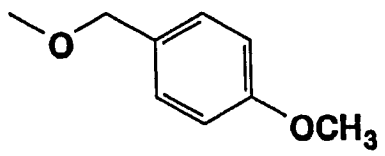
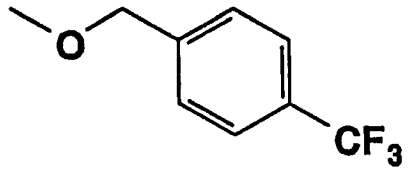
The following compounds of the general formula:-

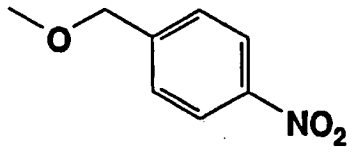
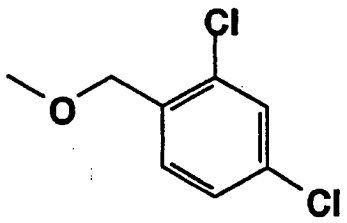


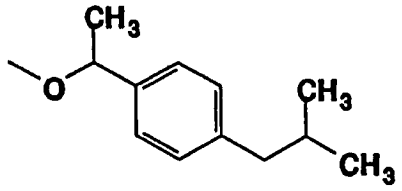
were prepared by alkylation of the corresponding phenol derivatives (see Preparation 4 and Example 37) with the corresponding alkyl bromides (see, e.g., Preparations 11 to 13) by similar methods to that used in illustrative Method 2.

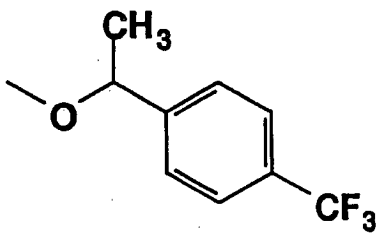
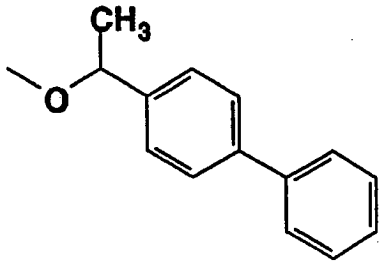
Example No.	X	R^7	m.p. (°C)	m/z	Analysis/NMR
19	CH_2		-	526 $(M+1)^+$	^{1}H-NMR ($CDCl_3$): δ = 0.90 (d,6H), 1.30(t,3H), 1.60(d,3H), 1.85(m,1H), 2.20(m,2H), 2.30(t,2H), 2.45(d,2H), 4.10(s,2H), 4.15(q,2H), 4.25(t,2H), 5.25(q,1H), 6.85(d,2H), 7.10(d,2H), 7.15(d,2H), 7.20-7.40(m,5H), 7.75 (s,1H), 8.46(m,1H) ppm.
20	CH_2		-	532 $(M+1)^+$	Found: C,79.00; H,6.07; N,2.54; $C_{35}H_{33}NO_4$ requires: C,79.07; H,6.26; N,2.63%. ^{1}H-NMR ($CDCl_3$): δ = 1.30 (t,3H), 2.25(m,2H), 2.35 (t,2H), 4.15(s,2H), 4.20 (q,2H), 4.25(t,2H), 5.10 (s,2H), 6.95(d,2H), 7.25-7.65(m,14H), 7.80(s,1H), 8.45(m,1H) ppm.

Example No.	X	R^7	m.p. (°C)	m/z	Analysis/NMR
21	CH_2		-	524 (M+)	^{1}H-NMR ($CDCl_3$): δ = 1.25 (t,3H), 2.25(m,2H), 2.35 (t,2H), 4.15(s,2H), 4.20 (q,2H), 4.25(t,2H), 5.00 (s,2H), 6.95(d,2H), 7.25-7.55(m,8H), 7.82(s,1H), 8.45(m,1H) ppm.
22	CH_2		-	540 $(M+1)^+$	^{1}H-NMR ($CDCl_3$): δ = 0.95 (t,3H), 1.30(m,6H), 1.35- 2.10(m,6H), 2.20(m,2H), 2.30(t,2H), 2.55(t,2H), 4.05(s,2H), 4.15(q,2H), 4.25(t,2H), 5.05(m,1H), 6.80(d,2H), 7.15(m,4H), 7.25-7.40(m,5H), 7.75 (s,1H), 8.40(m,1H) ppm.

Example No.	X	R^7	m.p. (°C)	m/z	Analysis/NMR
23	CH_2		-	486 $(M+1)^+$	Found: C,72.26; H,6.24; N,3.12; $C_{30}H_{31}NO_5.3/4H_2O$ requires: C,72.20; H,6.56; N,2.81%. ^{1}H-NMR ($CDCl_3$): δ = 1.25 (t,3H), 2.20(m,2H), 2.30 (t,2H), 3.80(s,3H), 4.10 (s,2H), 4.15(q,2H), 4.25 (t,2H), 4.95(s,2H), 6.95 (m,4H), 7.20-7.40(m,7H), 7.80(s,1H), 8.40(m,1H) ppm.
24	CH_2		-	524 $(M+1)^+$	^{1}H-NMR ($CDCl_3$): δ = 1.25 (t,3H), 2.20(m,2H), 2.30 (t,2H), 4.05(s,2H), 4.10 (q,2H), 4.20(t,2H), 5.05 (s,2H), 6.90(d,2H), 7.24-7.60(m,9H), 7.80(s,1H), 8.40(m,1H) ppm.

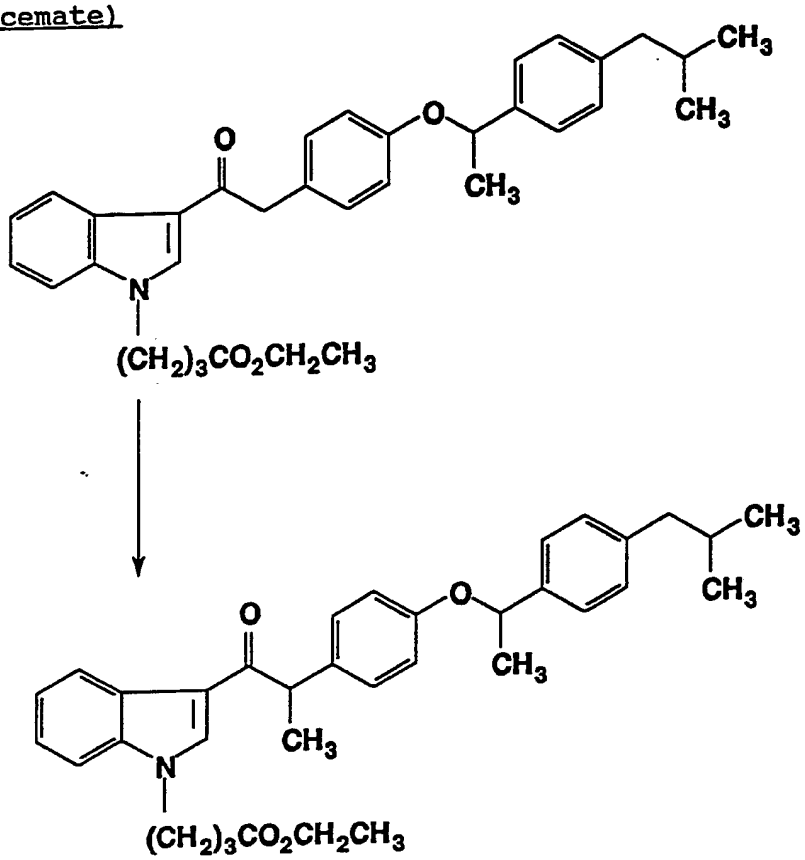
Example No.	X	R^7	m.p. (°C)	m/z	Analysis/NMR
25	CH_2		-	501 $(M+1)^+$	Found: C,69.24; H,5.50; N,5.49; $C_{29}H_{28}N_2O_6$ requires: C,69.59; H,5.64; N,5.60%. ^{1}H-NMR ($CDCl_3$): δ = 1.25 (t,3H), 2.20(m,2H), 2.30 (t,2H), 4.10(s,2H), 4.15 (q,2H), 4.25(t,2H), 5.15 (s,2H), 6.90(d,2H), 7.25-7.40(m,5H), 7.60(d,2H), 7.80(s,1H), 8.20(d,2H), 8.40(m,1H) ppm.
26	CH_2		-	524 (M+)	Found: C,66.35; H,5.26; N,2.88; $C_{29}H_{27}Cl_2NO_4$ requires: C,66.42; H,5.19; N,2.67%. ^{1}H-NMR ($CDCl_3$): δ = 1.15 (t,3H), 2.20(m,2H), 2.30 (t,2H), 4.10(s,2H), 4.20 (q,2H), 4.30(t,2H), 5.15 (s,2H), 6.90(d,2H), 7.25-7.50(m,8H), 7.80(s,1H), 8.40(m,1H) ppm.

Example No.	X	R^7	m.p. (°C)	m/z	Analysis/NMR
27	CH_2	$-OCH(CH_2CH_2CH_3)_2$	-	-	^{1}H-NMR ($CDCl_3$): δ = 0.95 (t,6H), 1.25(t,3H), 1.30-1.80(m,8H), 2.20(m,2H), 2.35(t,2H), 4.10(s,2H), 4.20(q,2H), 4.25(m,1H), 4.30(t,2H), 6.85(d,2H), 7.30-7.45(m,5H), 7.80 (s,1H), 8.40(m,1H) ppm.
28	$(CH_2)_2$		-	-	Found: C,77.82; H,7.78; N,2.56; $C_{35}H_{41}NO_4$ requires: C,77.89; H,7.66; N,2.60%. ^{1}H-NMR ($CDCl_3$): δ = 0.90 (d,6H), 1.25(t,3H), 1.62 (d,3H), 1.86(m,1H), 2.20 (m,2H), 2.32(t,2H), 2.45 (d,2H), 3.02(m,2H), 3.12 (m,2H), 4.15(q,2H), 4.25 (t,2H), 5.25(q,1H), 6.82 (d,2H), 7.10(d,4H), 7.25-7.45(m,5H), 7.70(s,1H), 8.40(m,1H) ppm.

Example No.	X	R^7	m.p. (°C)	m/z	Analysis/NMR
29	CH_2		-	538 (M^+)	^{1}H-NMR ($CDCl_3$): δ = 1.25(t,3H), 1.60(d,3H), 2.15(m,2H), 2.25(t,2H), 4.00(s,2H), 4.15(q,2H), 4.21(t,2H), 5.30(q,1H), 6.80(q,2H), 7.15(q,2H), 7.25-7.40(m,3H), 7.50(d,2H), 7.60(d,2H), 7.77(s,1H), 8.40(m,1H) ppm.
30	CH_2		-	546 (M^+)	^{1}H-NMR ($CDCl_3$): δ = 1.24(t,3H), 1.65(d,3H), 2.18(m,2H), 2.30(t,2H), 4.00(s,2H), 4.11(q,2H), 4.19(t,2H), 5.31(q,1H), 6.85(d,2H), 7.20(d,2H), 7.28-7.60(m,12H), 7.75(s,1H), 8.40(m,1H) ppm.

EXAMPLE 31

4-(3-[2-(4-[1-(4-[2-Methylpropyl]phenyl)ethoxy]-phenyl)propanoyl]indol-1-yl)butanoic acid ethyl ester (racemate)

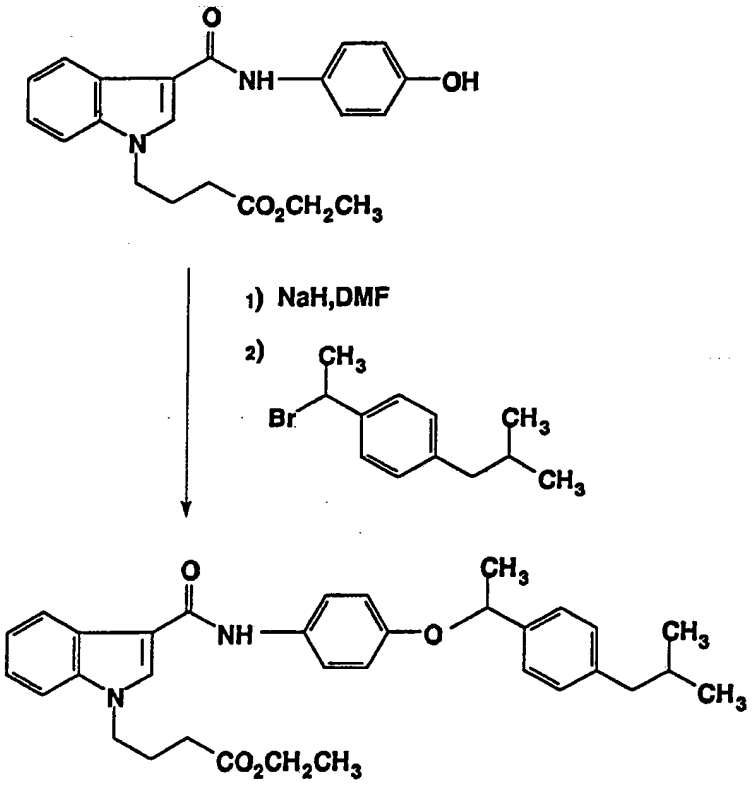


A solution of (R,S)-4-[3-(4-[1-(4-[2-methylpropyl]phenyl)ethoxy]phenylethanoyl)indol-1-yl]butanoic acid ethyl ester (see Example 19) (522mg) in DMF (5ml) was treated with sodium hydride (60% dispersion in oil, 43mg) and stirred at room temperature for 10 minutes. Methyl iodide (62μl) was added and stirring was continued for 16 hours at room temperature. The mixture was diluted with ethyl acetate (30ml) and washed with 1N hydrochloric acid solution (30ml) and water (30ml). The organic layer was dried ($MgSO_4$) and evaporated to give a yellow oil which was purified by flash chromatography (silica, 3:1 hexane/ethyl acetate) to give, after evaporation of the appropriate fractions, the title compound as a yellow oil (247mg).

^{1}H-NMR ($CDCl_3$): δ = 0.90(d,6H), 1.30(t,3H), 1.50(d,2H), 1.55(d,3H), 1.80(m,1H), 2.15(m,2H), 2.24(m,2H), 2.40(m,2H), 4.10(m,4H), 4.38(q,1H), 5.20(q,1H), 6.78(d,2H), 7.05(d,2H), 7.10-7.40(m,7H), 7.62(d,1H), 8.40(m,1H) ppm.

EXAMPLE 32

(R,S)-4-(3-[N-(4-[1-(4-[2-Methylpropyl]phenyl)-ethoxy]phenyl)carbamoyl]indol-1-yl)butanoic acid ethyl ester



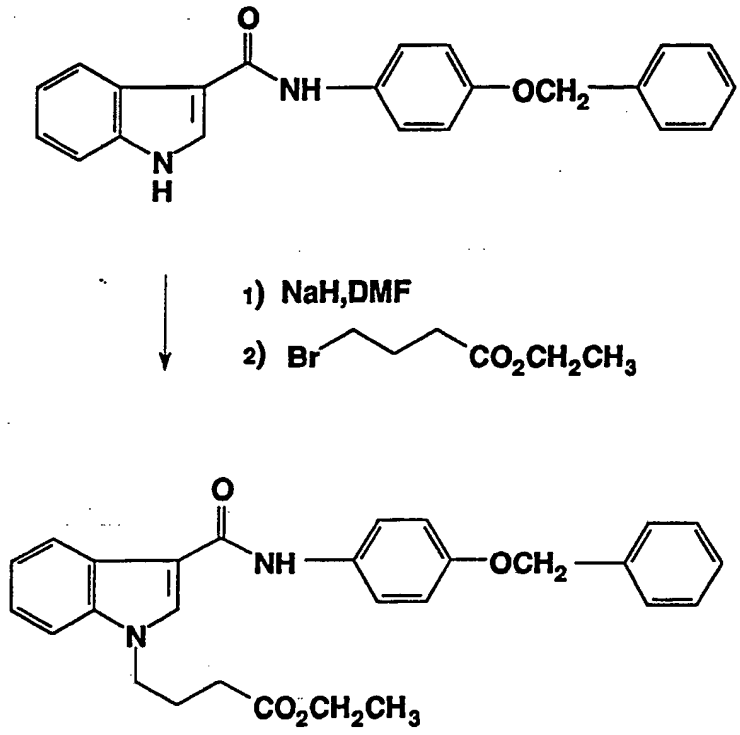
A solution of 4-(3-[N-(4-hydroxyphenyl)carbamoyl]-indol-1-yl)butanoic acid ethyl ester (see Preparation 2) (220mg) in DMF (5ml) was treated with sodium hydride (60% dispersion in oil, 26mg). After stirring for 30 minutes a solution of α-methyl-4-(2-methylpropyl)benzyl bromide (see Preparation 12) (174mg) in DMF (2ml) was added and stirring continued for 45 minutes. The mixture was diluted with ethyl acetate (30ml) and washed successively with 2N hydrochloric acid solution (50ml), water (5 x 30ml) and saturated brine (2 x 30ml).

The organic layer was dried ($MgSO_4$) and evaporated to give a yellow oil (265mg). Flash chromatography (silica, 3:1 hexane/ethyl acetate) gave, after evaporation of the appropriate fractions, the title compound as a gum which crystallised from diethyl ether, (193mg), m.p. 101-103°C. Found: C,75.56; H,6.97; N,5.39; $C_{33}H_{38}N_2O_4$ requires: C,75.30; H,7.28; N,5.32%.

^{1}H-NMR ($CDCl_3$): δ = 0.90(d,6H), 1.25(t,3H), 1.60(d,3H), 1.81(m,1H), 2.15(m,2H), 2.30(t,2H), 2.45(d,2H), 4.10(q,2H), 4.20(t,2H), 5.25(q,1H), 6.85(d,2H), 7.10(d,2H), 7.25-7.50(m,7H), 7.55(s,1H), 7.75(s,1H), 8.00(m,1H) ppm.

EXAMPLE 33

4-(3-[N-(4-Benzyloxyphenyl)carbamoyl]indol-1-yl)butanoic acid ethyl ester

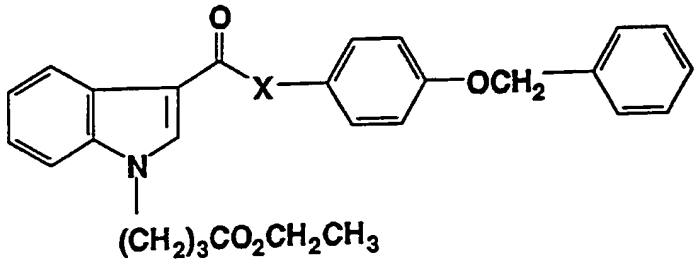


A solution of 3-(N-[4-benzyloxyphenyl]carbamoyl)-1H-indole (see Preparation 3) (4.0g) in DMF (60ml) was added to a suspension of sodium hydride (60% dispersion in oil, 515mg) in DMF (20ml). After stirring for 30 minutes at 20°C a solution of ethyl 4-bromobutyrate (2.52g) in DMF (20ml) was added. After stirring for 30 minutes at 20°C the DMF was removed in vacuo. The resultant off-white solid was triturated with ethyl acetate and filtered. The filtrate was absorbed onto silica gel and chromatographed (silica, 1:1 ethyl acetate/hexane) to give, after evaporation of the appropriate fractions, the desired product, (850mg), m.p. 124-126°C. Found: C,73.91; H,6.38; N,6.14; $C_{28}H_{28}N_2O_4$ requires: C,73.66; H,6.18; N,6.13%.

^{1}H-NMR ($CDCl_3$): δ = 1.20(t,3H), 2.15(m,2H), 2.25(t,2H), 4.10(q,2H), 4.20(t,2H), 5.04(s,2H), 6.95(d,2H), 7.25-7.50(m,8H), 7.55(d,2H), 7.65(s,1H), 7.75(s,1H), 8.05(m,1H) ppm.

EXAMPLES 34 to 36

The following compounds of the general formula:-



were prepared by similar methods to that used in Example 33 using the corresponding 1H-indoles (see Preparations 4 to 6) and ethyl 4-bromobutyrate as the starting materials.

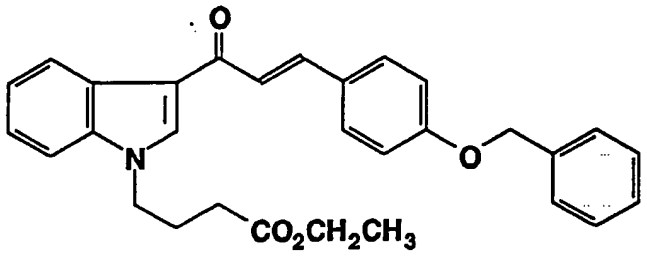
Example No.	X	m.p. (°C)	m/z	Analysis/NMR
34	O	96-97	-	Found: C,73.07; H,5.87; N,3.03; $C_{28}H_{27}NO_5$ requires: C,73.34; H,5.94; N,3.05%. ^{1}H-NMR ($CDCl_3$): δ = 1.30 (t,3H), 2.25(m,2H), 2.40 (t,2H), 4.20(q,2H), 4.35 (t,2H), 5.10(s,2H), 7.05 (d,2H), 7.20(d,2H), 7.30-7.50(m,8H), 8.00(s,1H), 8.30(m,1H) ppm.
35	CH=CH (trans)	83-84	468 $(M+1)^+$	Found: C,77.00; H,6.11; N,3.01; $C_{28}H_{25}NO_4$ requires: C,77.06; H,6.25; N,3.00%. ^{1}H-NMR ($CDCl_3$): δ = 1.28 (t,3H), 2.30 (m,2H), 2.40(m,2H), 4.20 (m,2H), 4.35(m,2H), 5.15 (s,2H), 7.02(d,2H), 7.28-7.55 (m,9H), 7.65(d,2H), 7.84 (d,1H), 7.94 (s,1H), 8.55(m,1H) ppm.

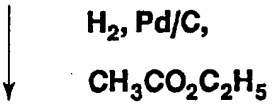
Example No.	X	m.p. (°C)	m/z	Analysis/NMR
36[1]	CH_2	-	-	Found: C,76.22; H,6.29; N,2.98; $C_{29}H_{29}NO_4$ requires: C,76.46; H,6.42; N,3.07%. ^{1}H-NMR ($CDCl_3$): δ = 1.30 (t,3H), 2.20(m,2H), 2.35 (t,2H), 4.10(s,2H), 4.15 (q,2H), 4.25(t,2H), 5.05 (s,2H), 6.95(d,2H), 7.25-7.45(m,10H), 7.80(s,1H), 8.45(m,1H) ppm.

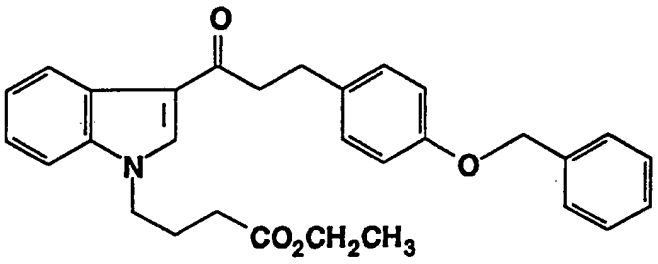
1 The reaction mixture work-up was to add 1N hydrochloric acid solution and extract the mixture with ethyl acetate. The organic layer was washed with brine and then water, dried and concentrated in vacuo to provide the required product. The chromatographic work-up used in Example 33 was hence unnecessary.

EXAMPLE 37

4-(3-[3-(4-Benzyloxyphenyl)propanoyl]indol-1-yl)butanoic acid ethyl ester







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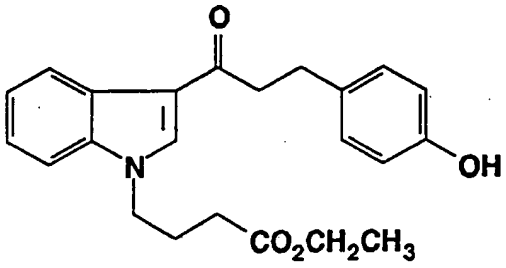


A solution of (E)-4-(3-[3-(4-benzyloxyphenyl)-propenoyl]indol-1-yl)butanoic acid ethyl ester (see Example 35) (1g) in ethyl acetate (25ml) was hydrogenated in the presence of 10% palladium-on-charcoal (250mg) at 4.15×10^5 Pa for 4.5 hours. The reaction was filtered through a cellulose-based filter aid and the filtrate concentrated in vacuo. The residual oil was chromatographed (silica, 40% ethyl acetate/hexane) to first provide, after combination and evaporation of the appropriate fractions, the title compound, (580mg), m.p. 123-5°C, m/z = 442 $(M+1)^+$. Found: C,75.89; H,6.20; N,3.17; $C_{28}H_{27}NO_4$ requires: C,76.17; H,6.16; N,3.17%.

^{1}H-NMR (d_6-DMSO): δ = 2.00 (quintet,2H), 2.25(t,2H), 2.90(t,2H), 3.12(t,2H), 4.25(t,2H), 5.05(s,2H), 6.90(d,2H), 7.20-7.48(m,9H), 7.60(d,1H), 8.20(d,1H), 8.40(s,1H), 12.25(s,br,1H) ppm.

Further elution provided, after combination and evaporation of the appropriate fractions, 4-(3-[3-(4-hydroxyphenyl)propanoyl]indol-1-yl)butanoic acid ethyl ester, (240mg).

^{1}H-NMR ($CDCl_3$): δ = 1.25(t,3H), 2.14(quintet,2H), 2.28(t,2H), 3.02(m,2H), 3.12(m,2H), 4.02-4.26(m,4H), 5.62(s,1H), 6.75(d,2H), 7.10(d,2H), 7.22-7.40(m,3H), 7.54(s,1H), 8.40(m,1H) ppm.

The following Preparations illustrate the preparation of certain starting materials used in the previous Examples:-

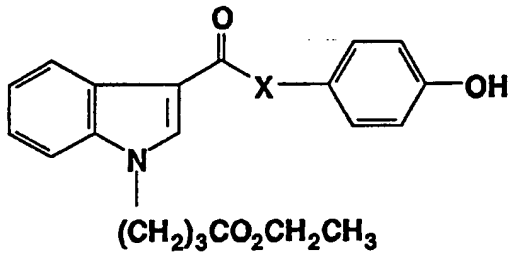
ILLUSTRATIVE METHOD 3

4-(3-[4-Hydroxybenzoyl]indol-1-yl)butanoic acid ethyl ester

A solution of 4-(3-[4-benzyloxybenzoyl]indol-1-yl)butanoic acid ethyl ester (13.4g) in ethyl acetate (300ml) was hydrogenated at 4.15 x 10^5 Pa in the presence of 10% palladium-on-charcoal (3g) at room temperature for 4 hours. The catalyst was removed by filtration of the reaction through a cellulose-based filter aid and the filtrate was concentrated in vacuo to a pale pink solid. Trituration with cold diethyl ether gave a white powder, (8.24g).

PREPARATIONS 1 and 2

The following compounds of the general formula:-



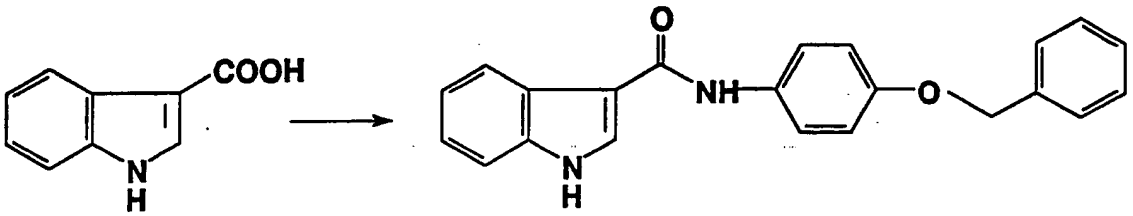
were prepared by hydrogenation of the corresponding benzyl ethers (see Examples 33 and 36) by similar methods to that used in illustrative Method 3.

Prep. No.	X	m.p. (°C)	m/z	Analysis/NMR
1	CH_2	-	366 $(M+1)^+$	^{1}H-NMR ($CDCl_3$): δ = 1.25(t,3H), 2.20(m,2H), 2.35(t,2H), 4.10(s,2H), 4.15(q,2H), 4.25(t,2H), 6.80(d,2H), 7.20(d,2H), 7.25-7.45(m,3H), 7.75(s,1H), 8.40(m,1H) ppm.
2[1]	NH	193-196	-	Found: C,68.88; H,5.98; N,7.40; $C_{21}H_{22}N_2O_4$ requires: C,68.83; H,6.05; N,7.64%. ^{1}H-NMR (d_6-DMSO): δ = 1.05(t,3H), 2.00(m,2H), 2.15(t,2H), 3.90(q,2H), 4.05(t,2H), 6.60(d,2H), 7.10(m,2H), 7.25(d,1H), 7.30(d,2H), 7.75(s,1H), 8.05(d,1H), 8.45(s,1H), 8.55(s,1H) ppm.

1 Hydrogenation carried out at 40°C.

PREPARATION 3

3-(N-[4-Benzyloxyphenyl]carbamoyl)-1H-indole

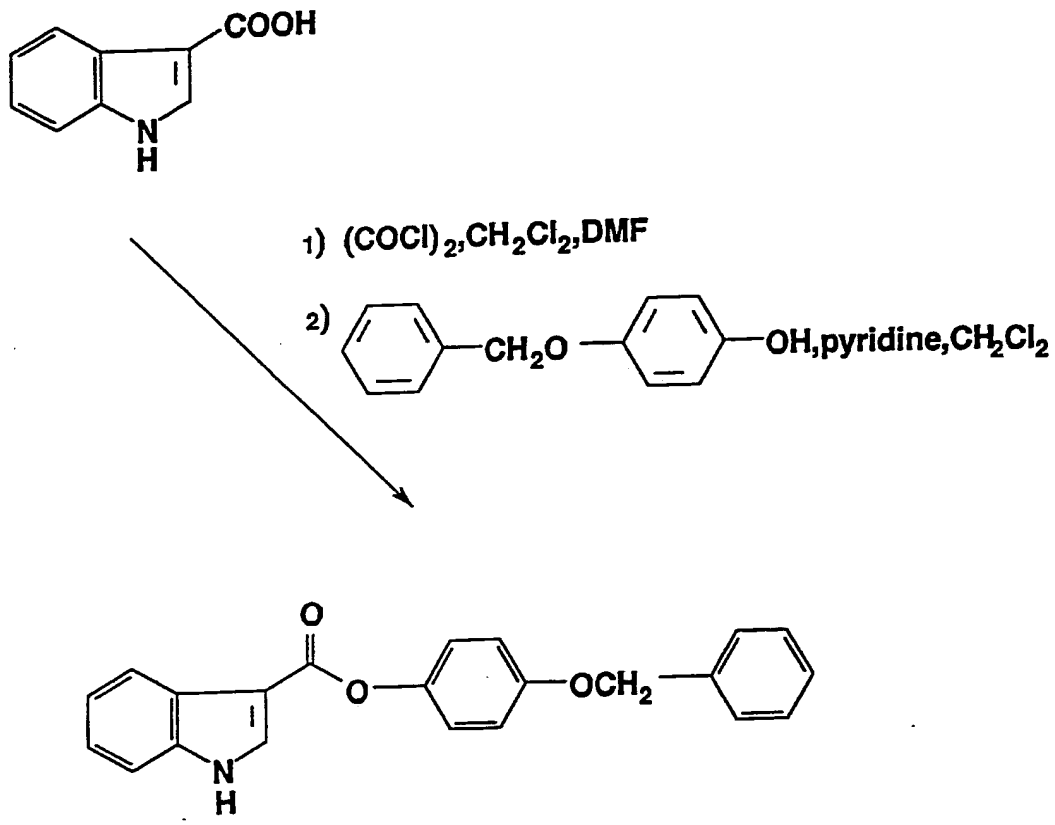


A stirred solution of 1H-indole-3-carboxylic acid (6.0g) in dichloromethane (100ml) was treated with 1-hydroxybenzotriazole hydrate (5.0g) and 1-(3-N,N-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (14.2g) followed by triethylamine (21ml) and 4-benzyloxyaniline hydrochloride (9.65g). The mixture was stirred at room temperature for 2 hours, diluted with dichloromethane and washed successively with water (2 x 100ml), 2N hydrochloric acid (4 x 100ml) and saturated aqueous brine (2 x 50ml). The organic layer was dried (Na_2SO_4), filtered and evaporated. During the evaporation the desired product crystallised as a white solid and was collected by filtration (5.89g). The mother liquors were evaporated to a pale brown oil and chromatographed (silica, 1:1 ethyl acetate/hexane) to give a further crop of the desired product, (995mg), m.p. 211-214°C.
Found: C,77.55; H,5.51; N,8.26; $C_{22}H_{18}N_2O_2$ requires: C,77.18; H,5.30; N,8.18%.

^{1}H-NMR (d_6-DMSO): δ = 5.05(s,2H), 6.95(d,2H), 7.10(m,2H), 7.25-7.45(m,6H), 7.60(d,2H), 8.10(s,1H), 8.15(d,1H), 9.60(s,1H), 11.70(s,br,1H) ppm.

PREPARATION 4

1H-Indole-3-carboxylic acid 4-benzyloxyphenyl ester



A suspension of 1H-indole-3-carboxylic acid (10g) in dichloromethane (250ml) was cooled to 0°C and treated with oxalyl chloride (8.9ml) and dimethylformamide (DMF) (5 drops). After stirring for one hour the clear solution was evaporated and azeotroped three times with dichloromethane to give the acid chloride as a brown crystalline solid.

To a solution of 4-benzyloxyphenol (12.40g) in dichloromethane (200ml) was added pyridine (7.5ml) followed by a solution of the acid chloride prepared above in dichloromethane (200ml). After stirring overnight the mixture was evaporated and partitioned between ethyl acetate (100ml) and 2N hydrochloric acid (50ml). The separated organic layer was washed with 2N hydrochloric acid (2 x 50ml) and then saturated brine (2 x 50ml). The organic layer was dried ($MgSO_4$), evaporated and the residue crystallised from dichloromethane to give the title compound as a white solid, (19.57g), m.p. 188-189°C.
Found: C,77.07; H,4.77; N,4.05; $C_{22}H_{17}NO_3$ requires: C,76.95; H,4.99; N,4.08%.

^{1}H-NMR ($CDCl_3$): δ = 4.90(s,2H), 6.85(d,2H), 7.00(d,2H), 7.05-7.40(m,8H), 7.90(s,1H), 8.00(m,1H), 11.00(s,br,1H) ppm.

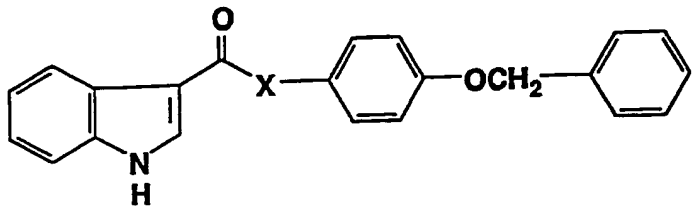
ILLUSTRATIVE METHOD 4

3-(4-Benzyloxybenzoyl)-1H-indole

A mechanically stirred solution of indole (30.0g) in sodium dried diethyl ether (450ml) was treated dropwise with methylmagnesium iodide (85ml of 3.0M solution in diethyl ether). After stirring for one hour at 20°C 4-benzyloxybenzoyl chloride (67.3g) was added. Stirring was continued for two hours at 20°C and then 1N hydrochloric acid (250ml) added to the mixture and the reaction was allowed to stand overnight. The resulting precipitate was filtered off and triturated with hot ethyl acetate (3 x 100ml) to give the desired compound as a pale pink solid, (40.9g).

PREPARATIONS 5 and 6

The following indoles of the general formula:-



were prepared from 1H-indole and the corresponding acid chlorides (see Preparations 7 and 8) using similar methods to that used in illustrative Method 4.

Prep. No.	X	m.p. (°C)	m/z	Analysis/NMR
5	CH_2	-	341 (M^+)	^{1}H-NMR (d_6-DMSO): δ = 4.00(s,2H), 5.00(s,2H), 6.90(d,2H), 7.10-7.40(m,10H), 8.10(d,1H), 8.45(s,1H), 12.00(s,br,1H) ppm.
6	CH=CH (trans)	-	354 $(M+1)^+$	^{1}H-NMR (d_6-DMSO): δ = 5.15(s,2H), 7.00-7.80(m,14H), 8.30(d,1H), 8.65(d,1H) ppm.

ILLUSTRATIVE METHOD 5

4-Benzyloxy-2,3-dimethylbenzoyl chloride

4-Benzyloxy-2,3-dimethylbenzoic acid (2.0g) was suspended in dichloromethane (10ml) and treated with oxalyl chloride (1.3ml) and dimethylformamide (DMF) (2 drops). After stirring overnight the homogeneous solution was evaporated to give a white solid which was azeotroped three times with toluene to give the title compound as a white powder (2.24g).

PREPARATION 7

4-Benzyloxyphenacyl chloride

The title compound was prepared using a similar method to that described in illustrative Method 5 except using 4-benzyloxyphenylacetic acid as the starting material. The material obtained was used immediately.

PREPARATION 8

(E)-3-(4-Benzyloxyphenyl)propenoyl chloride

The title compound was prepared using a similar method to that described in illustrative Method 5 except using (E)-3-(4-benzyloxyphenyl)propenoic acid as the starting material. The material obtained was used immediately.

PREPARATION 9

1-(4-n-Propylphenyl)butan-1-ol

A solution of 4-n-propylbenzaldehyde (7.4g) in diethyl ether (60ml) was cooled to 0°C and treated with a 2.0M solution of n-propylmagnesium chloride in diethyl ether (27.5ml). The reaction was stirred overnight, diluted with diethyl ether and quenched with saturated aqueous ammonium chloride solution. The organic layer was separated, washed with saturated aqueous ammonium chloride solution and dried ($MgSO_4$). The organic layer was filtered and evaporated to give a colourless oil which was purified by chromatography (silica, 4:1 hexane/ethyl acetate) to provide, after evaporation of the appropriate fractions, the desired product, (4.06g), $m/z = 192(M^+)$.

^{1}H-NMR ($CDCl_3$): δ = 1.00(m,6H), 1.20-1.40(m,2H), 1.70(q,2H), 1.75-1.90(m,3H), 2.60(t,2H), 4.60(m,1H), 7.10(d,2H), 7.30(d,2H) ppm.

PREPARATION 10

(R,S)-1-(4-[2-Methylpropyl]phenyl)ethanol

A solution of 4-isobutyrylacetophenone (10.0g) in methanol (50ml) was cooled to 0°C and treated portionwise with sodium borohydride (3.23g). After stirring overnight at room temperature the reaction was quenched with 1N hydrochloric acid (50ml) and ethyl acetate (100ml) added. The organic layer was separated, dried ($MgSO_4$) and evaporated to give the title compound as a clear oil, (10.02g), m/z = 178(M^+). Found: C,79.69; H,9.90; $C_{12}H_{18}O$.1/7 H_2O requires: C,79.68; H,10.19%.

^{1}H-NMR ($CDCl_3$): δ = 0.90(d,6H), 1.50(d,3H), 1.85(m,1H), 2.50(d,2H), 4.85(q,1H), 7.15(d,2H), 7.30(d,2H) ppm.

PREPARATIONS 11 to 13

The following alkyl bromides were prepared by dissolving the corresponding alcohol (see, e.g., Preparations 9 and 10) in dichloromethane and cooling the solution in an ice-bath whilst saturating with dry hydrogen bromide. After stirring the mixture for a short period the reaction was evaporated in vacuo to provide the desired alkyl bromide which was used directly without characterisation.

Preparation No.	Alkyl bromide
11	1-Bromo-1-(4-n-propylphenyl)butane.
12	α-Methyl-4-(2-methylpropyl)benzyl bromide.
13[1]	α-(4-n-Propylphenyl)-4-n-propylbenzyl bromide.

[1] For starting material see EP-A-291245.

Pharmacological activity

A selection of compounds of the formula (I) was tested in vitro for steroid 5α-reductase inhibitory activity using ventral prostate tissue from male rats according to the procedure outlined on pages 33 to 35 of the specification. The results obtained are presented in Table 1.

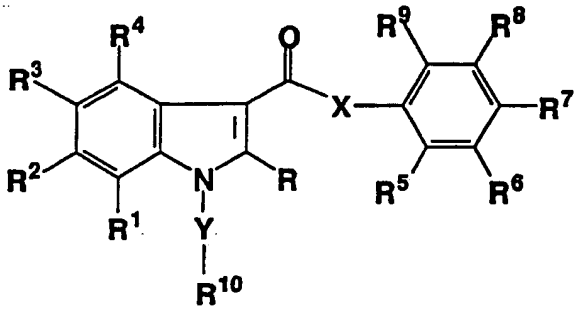
Table 1

Example No.	IC_{50}(nM)
1	42.6
2	321
3	300
4	39.7
5	1000
6	1000
7	300
8	1780
9	316
10	1400
11	1260
12	64
13	147
14	186
15	276
16	140
17	39.2
18	191

In addition, the compound of Example 36 was tested in vitro for steroid 5α-reductase inhibitory activity using tissue from hyperplastic human prostates by the procedure outlined on pages 35 to 37 of the specification. An IC_{50} value of 89.7nM was obtained for this compound.

CLAIMS

1. A compound of the formula:-



....(I)

or a pharmaceutically acceptable salt thereof,

wherein X is O, NH, N(C_1-C_4 alkyl), C_1-C_4 alkylene, C_2-C_4 alkenylene or C_2-C_4 alkynylene, said alkylene, alkenylene and alkynylene groups being optionally substituted by C_1-C_4 alkyl or aryl;

Y is C_1-C_6 alkylene optionally substituted by C_1-C_6 alkyl;

R is H, OH, halo, C_1-C_4 alkyl or C_1-C_4 alkoxy;

R^1, R^2, R^3 and R^4 are each independently selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, OH, halo and CF_3;

one of R^6, R^7 and R^8 is C_1-C_{15} alkyl or a group of the formula -Z(C_1-C_{15} alkyl), -Z(aryl) or -Z(C_3-C_7 cycloalkyl), said alkyl group being optionally interrupted by O, $S(O)_q$, NH or N(C_1-C_6 alkyl), and said alkyl group and the alkyl group of said -Z(C_1-C_{15} alkyl) group being optionally substituted by C_1-C_{10} alkoxy, aryl, C_3-C_7 cycloalkyl or a group of the formula

-Z(aryl), and the remainder of R^6, R^7 and R^8 and R^5 and R^9 are each independently selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, halo and halo(C_1-C_4 alkyl);
R^{10} is COOH, $COOR^{11}$ or $CONR^{12}R^{13}$;
R^{11} is a biolabile ester-forming group;
R^{12} and R^{13} are each independently selected from H and C_1-C_4 alkyl;
Z is O, $S(O)_q$, NH or N(C_1-C_6 alkyl);
q is 0, 1 or 2;
and "aryl", used in the definitions of X, R^6, R^7 and R^8, means phenyl optionally substituted by C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl, OH, halo, CF_3, halo(C_1-C_6 alkyl), nitro, amino, C_2-C_6 alkanamido, C_2-C_6 alkanoyl or phenyl.

2. A compound as claimed in claim 1 wherein X is O, NH, C_1-C_4 alkylene or C_2-C_4 alkenylene;
Y is C_1-C_6 alkylene;
R is H or C_1-C_4 alkyl;
R^1, R^2, R^3 and R^4 are each H;
one of R^6, R^7 and R^8 is -O(C_1-C_{15} alkyl), the alkyl of said -O(C_1-C_{15} alkyl) group being optionally substituted by aryl, and the remainder of R^6, R^7 and R^8 and R^5 and R^9 are each H;
R^{10} is COOH or $COOR^{11}$; and
"aryl" means phenyl optionally substituted by from 1 to 3 substituents each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CF_3, nitro and phenyl.

3. A compound as claimed in claim 2
wherein X is O, NH, methylene, ethylene or ethenylene;
Y is propylene;
R is H;
one of R^6, R^7 and R^8 is $-OCH_2$(aryl) or $-OCH(C_1-C_4$ alkyl)(aryl) and the remainder of R^6, R^7 and R^8 and R^5 and R^9 are each H; and
R^{10} is COOH or $COO(C_1-C_6$ alkyl).

4. A compound as claimed in claim 3
wherein X is methylene;
R^7 is $-OCH(CH_3)$(aryl) and R^5, R^6, R^8 and R^9 are each H;
R^{10} is COOH or $COOC_2H_5$; and
"aryl" means phenyl optionally substituted by 1 or 2 substituents each independently selected from n-propyl, isobutyl, methoxy, chloro, CF_3, nitro or phenyl.

5. A compound as claimed in claim 4
wherein R^{10} is COOH and "aryl" means phenyl, 4-(n-propyl)phenyl, 4-isobutylphenyl, 4-methoxyphenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 4-trifluoromethylphenyl, 4-nitrophenyl or 4-phenylphenyl.

6. A compound as claimed in claim 5
wherein "aryl" means 4-isobutylphenyl.

7. (R,S)-4-(3-[4-(1-[4-(2-Methylpropyl)phenyl]ethoxy)-phenylethanoyl]indol-1-yl)butanoic acid or
(S)-4-(3-[4-(1-[4-(2-Methylpropyl)phenyl]ethoxy)-phenylethanoyl]indol-1-yl)butanoic acid: or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition comprising a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of the preceding claims, together with a pharmaceutically acceptable diluent or carrier.

9. A compound of the formula (I), or a pharmaceutically acceptable salt or composition thereof, as claimed in any one of claims 1 to 7 and 8 respectively, for use as a medicament.

10. The use of a compound of the formula (I), or of a pharmaceutically acceptable salt or composition thereof, as claimed in any one of claims 1 to 7 and 8 respectively, for the manufacture of a medicament for inhibiting a steroid 5α-reductase.

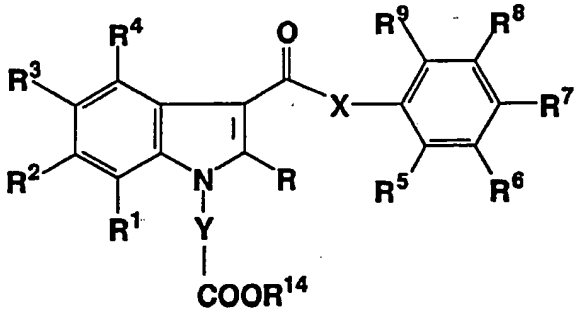
11. The use of a compound of the formula (I), or of a pharmaceutically acceptable salt or composition thereof, as claimed in any one of claims 1 to 7 and 8 respectively, for the manufacture of a medicament for the curative or prophylactic treatment of acne vulgaris, alopecia, seborrhoea, female hirsutism, benign prostatic hypertrophy or male pattern baldness.

12. The use of a compound of the formula (I), or of a pharmaceutically acceptable salt or composition thereof, as claimed in any one of claims 1 to 7 and 8 respectively, for the manufacture of a medicament for the curative or prophylactic treatment of a human prostate adenocarcinoma.

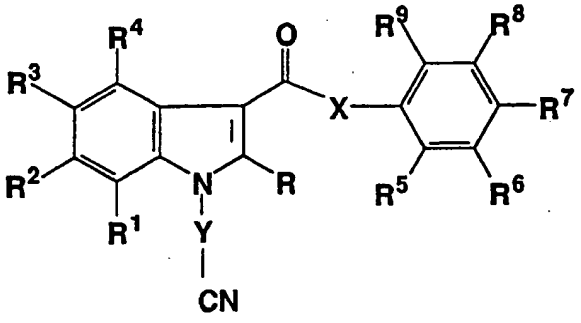
13. A method of treatment of a human to inhibit a steroid 5α-reductase which comprises treating said human with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt or composition thereof as claimed in any one of claims 1 to 7 and 8 respectively.

14. A method of treatment of a human to cure or prevent acne vulgaris, alopecia, seborrhoea, female hirsutism, benign prostatic hypertrophy, male pattern baldness or a human prostate adenocarcinoma which comprises treating said human with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt or composition thereof as claimed in any one of claims 1 to 7 and 8 respectively.

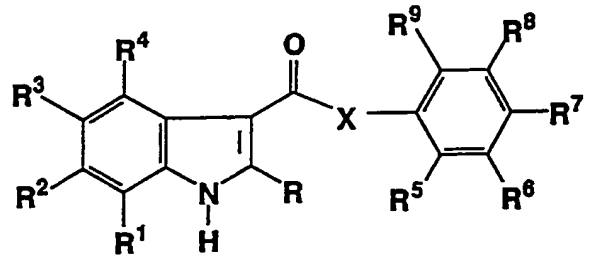
15. A compound of the formula:-



....(II) ;

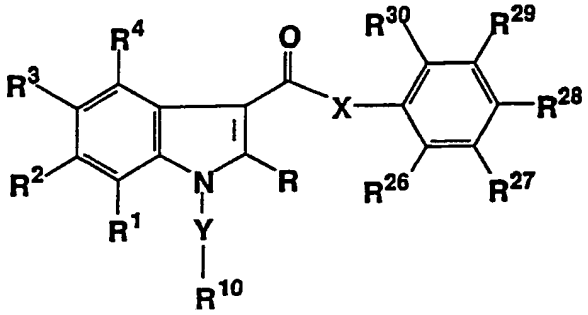


....(IV) ;



....(VIII)

or a base salt thereof; or

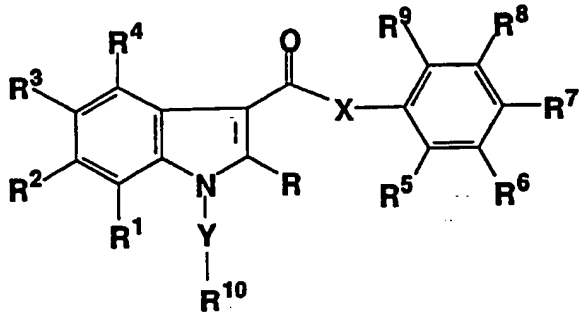


....(XIX)

or a base salt thereof:

wherein X, Y, R and R^1 to R^{10} are as defined in claim 1, R^{14} is an ester-forming group that may be cleaved to provide a compound of the formula (I) wherein R^{10} is COOH with the proviso that R^{14} is not as defined for R^{11} in claim 1, one of R^{27}, R^{28} and R^{29} is a group of the formula $-Z^7-H$ wherein Z^7 is O, S, NH or $N(C_1-C_6$ alkyl) and the remainder of R^{27}, R^{28} and R^{29} are as defined in claim 1 for the remainder of R^6, R^7 and R^8, and R^{26} and R^{30} are as defined in claim 1 for R^5 and R^9.

16. A process for the preparation of a compound of the formula:-



....(I)

or a pharmaceutically acceptable salt thereof,

wherein X is O, NH, N(C_1-C_4 alkyl), C_1-C_4 alkylene, C_2-C_4 alkenylene or C_2-C_4 alkynylene, said alkylene, alkenylene and alkynylene groups being optionally substituted by C_1-C_4 alkyl or aryl;

Y is C_1-C_6 alkylene optionally substituted by C_1-C_6 alkyl;

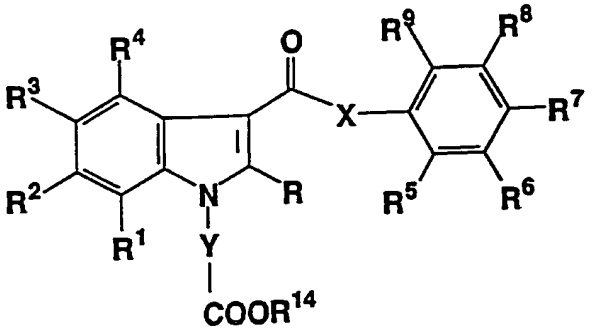
R is H, OH, halo, C_1-C_4 alkyl or C_1-C_4 alkoxy;

R^1, R^2, R^3 and R^4 are each independently selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, OH, halo and CF_3;

one of R^6, R^7 and R^8 is C_1-C_{15} alkyl or a group of the formula -Z(C_1-C_{15} alkyl), -Z(aryl) or -Z(C_3-C_7 cycloalkyl), said alkyl group being optionally interrupted by O, $S(O)_q$, NH or N(C_1-C_6 alkyl), and said alkyl group and the alkyl group of said -Z(C_1-C_{15} alkyl) group being optionally substituted by C_1-C_{10} alkoxy, aryl, C_3-C_7 cycloalkyl or a group of the formula -Z(aryl), and the remainder of R^6, R^7 and R^8 and R^5 and R^9 are each independently selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, halo and halo(C_1-C_4 alkyl);

R^{10} is COOH, $COOR^{11}$ or $CONR^{12}R^{13}$;
R^{11} is a biolabile ester-forming group;
R^{12} and R^{13} are each independently selected from H and C_1-C_4 alkyl;
Z is O, $S(O)_q$, NH or N(C_1-C_6 alkyl);
q is O, 1 or 2;
and "aryl", used in the definitions of X, R^6, R^7 and R^8, means phenyl optionally substituted by C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl, OH, halo, CF_3, halo(C_1-C_6 alkyl), nitro, amino, C_2-C_6 alkanamido, C_2-C_6 alkanoyl or phenyl, which comprises,

(a) for the preparation of a compound of the formula (I) wherein R^{10} is COOH and X, Y, R and R^1 to R^9 are as previously defined for a compound of the formula (I), cleavage of an ester of the formula:-

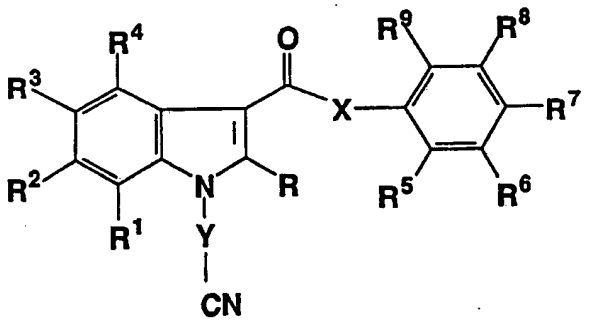


....(II)

wherein R^{14} is an ester-forming group that may be cleaved to provide a compound of the formula (I) wherein R^{10} is COOH and X, Y, R and R^1 to R^9 are as previously defined for a compound of the formula (I);

(b) for the preparation of a compound of the formula (I) wherein R^{10} is COOH and X, Y, R and R^1 to R^9 are as previously defined for a compound of the formula (I), acidic or basic hydrolysis of a compound of the formula (I) wherein R^{10} is $CONR^{12}R^{13}$ and X, Y, R, R^1 to R^9, R^{12} and R^{13} are as previously defined for a compound of the formula (I);

(c) for the preparation of a compound of the formula (I) wherein R^{10} is COOH and X, Y, R and R^1 to R^9 are as previously defined for a compound of the formula (I), acidic or basic hydrolysis of a compound of the formula:-



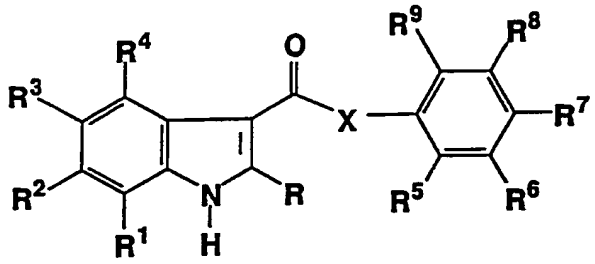
....(IV)

wherein X, Y, R and R^1 to R^9 are as previously defined for a compound of the formula (I);

(d) for the preparation of a compound of the formula (I) wherein R^{10} is $COOR^{11}$ and X, Y, R, R^1 to R^9 and R^{11} are as previously defined for a compound of the formula (I), esterification of a compound of the formula (I) wherein R^{10} is COOH and X, Y, R and R^1 to R^9 are as previously

defined for a compound of the formula (I), with an alcohol of the formula $R^{11}OH$ wherein R^{11} is as previously defined for a compound of the formula (I);

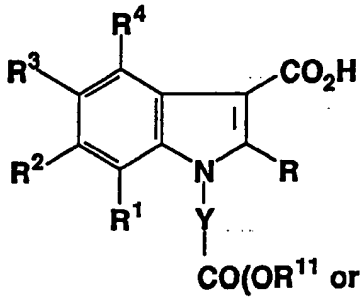
(e) for the preparation of a compound of the formula (I) wherein X, Y, R and R^1 to R^{10} are as previously defined for a compound of the formula (I), alkylation of a base salt of a compound of the formula:-



....(VIII)

wherein X, R and R^1 to R^9 are as previously defined for a compound of the formula (I), with a compound of the formula Z^3-Y-$COOR^{11}$ or Z^3-Y-$CONR^{12}R^{13}$ or with a base salt of a compound of the formula Z^3-Y-COOH, wherein Y, R^{11}, R^{12} and R^{13} are as previously defined for a compound of the formula (I) and Z^3 is a leaving group;

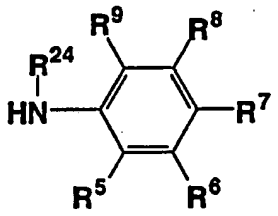
(f) for the preparation of a compound of the formula (I) wherein X is NH or N(C_1-C_4 alkyl), R^{10} is $COOR^{11}$ or $CONR^{12}R^{13}$ and Y, R, R^1 to R^9, R^{11}, R^{12} and R^{13} are as previously defined for a compound of the formula (I), reaction of a compound of the formula:-



....(XIII)

or an activated ester or imidazolide thereof,

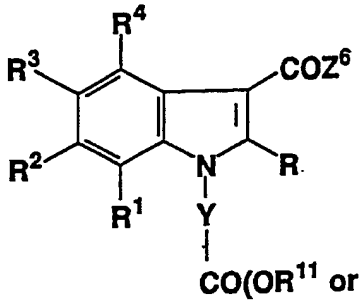
wherein Y, R, R^1 to R^4, R^{11}, R^{12} and R^{13} are as previously defined for a compound of the formula (I), with an amine of the formula:-



....(XVI)

wherein R^{24} is H or C_1-C_4 alkyl and R^5 to R^9 are as previously defined for a compound of the formula (I);

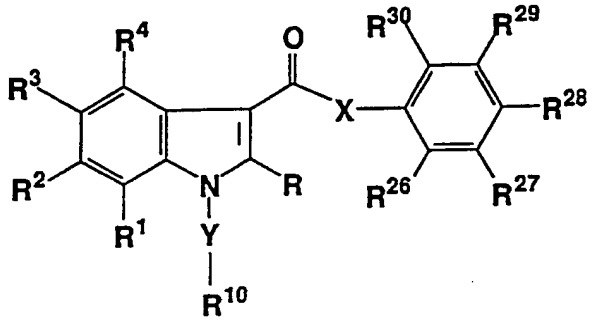
(g) for the preparation of a compound of the formula (I) wherein X, Y, R and R^1 to R^{10} are as defined in claim 16(f), reaction of a compound of the formula:-



....(XV)

wherein Y, R, R^1 to R^4, R^{11}, R^{12} and R^{13} are as previously defined for a compound of the formula (I) and Z^6 is a leaving group, with an amine of the formula (XVI) wherein R^{24} is H or C_1-C_4 alkyl and R^5 to R^9 are as previously defined for a compound of the formula (I);

h) for the preparation of a compound of the formula (I) wherein one of R^6, R^7 and R^8 is a group of the formula -Z(C_1-C_{15} alkyl) or -Z(C_3-C_7 cycloalkyl), the alkyl of said -Z(C_1-C_{15} alkyl) group being optionally substituted by C_1-C_{10} alkoxy, aryl, C_3-C_7 cycloalkyl or a group of the formula -Z(aryl), Z is O, S, NH or N(C_1-C_6 alkyl) and the remainder of R^6, R^7 and R^8, together with X, Y, R, R^1 to R^5, R^9, R^{10} and "aryl", are as previously defined for a compound of the formula (I), reaction of a compound of the formula:-



....(XIX)

or a base salt thereof,

wherein one of R^{27}, R^{28} and R^{29} is a group of the formula $-Z^7-H$ wherein Z^7 is O, S, NH or $N(C_1-C_6$ alkyl) and the remainder of R^{27}, R^{28} and R^{29} are as previously defined for the remainder of R^6, R^7 and R^8 for a compound of the formula (I), R^{26} and R^{30} are as previously defined for R^5 and R^9 for a compound of the formula (I) and X, Y, R, R^1 to R^4 and R^{10} are as previously defined for a compound of the formula (I), with a compound of the formula $R^{31}Z^8$ wherein R^{31} is C_1-C_{15} alkyl or C_3-C_7 cycloalkyl, said alkyl group being optionally substituted by C_1-C_{10} alkoxy, aryl, C_3-C_7 cycloalkyl or a group of the formula -Z(aryl), "aryl" and Z are as previously defined for this part (h) and Z^8 is a leaving group; or

(i) for the preparation of a compound of the formula (I) wherein R^{10} is $COOR^{11}$ or $CONR^{12}R^{13}$, one of R^6, R^7 and R^8 is a group of the formula $-O(C_1-C_{15}$ alkyl), -O(aryl) or $-O(C_3-C_7$ cycloalkyl), the alkyl of said $-O(C_1-C_{15}$ alkyl) group being optionally substituted by C_1-C_{10} alkoxy, aryl, C_3-C_7 cycloalkyl or a group of the formula -Z(aryl), and the remainder of R^6, R^7 and R^8, together with X, Y, Z, R, R^1 to R^5, R^9, R^{11}, R^{12}, R^{13} and "aryl", are as previously defined for a compound of the formula (I), reaction of a compound of the formula (XIX) wherein one of R^{27}, R^{28} and R^{29} is OH and the remainder of R^{27}, R^{28} and R^{29} and R^{26} and R^{30} are as defined in claim 16(h) and X, Y, R, R^1 to R^4 and R^{10} are as

previously defined for this part (i), with a compound of the formula $R^{32}OH$ wherein R^{32} is C_1-C_{15} alkyl, aryl or C_3-C_7 cycloalkyl, said alkyl group being optionally substituted by C_1-C_{10} alkoxy, aryl, C_3-C_7 cycloalkyl or a group of the formula -Z(aryl), wherein "aryl" and Z are as previously defined for a compound of the formula (I), in the presence of a dehydrating agent: any one of said processes (a) to (i) being optionally followed by conversion of the product of the formula (I) to a pharmaceutically acceptable salt thereof.

17. A process as claimed in claim 16(a) where the cleavage is carried out by acidic or basic hydrolysis of a compound of the formula (II).

18. A process as claimed in claim 17 wherein R^{14} is C_1-C_6 alkyl.

19. A process as claimed in claim 17 or 18 where the basic hydrolysis is carried out using sodium or potassium hydroxide under aqueous conditions.

20. A process as claimed in claim 16(e) where the base salt of a compound of the formula (VIII) is a sodium or potassium salt.

21. A process as claimed in claim 16(e) or 20 wherein Z^3 is halo, C_1-C_4 alkanesulphonyloxy or C_1-C_4 alkylphenylsulphonyloxy.

22. A process as claimed in claim 21 wherein Z^3 is bromo.

23. A process as claimed in claim 16(h) where a base salt of a compound of the formula (XIX) is used.

24. A process as claimed in claim 23 where the base salt is a sodium or potassium salt.

25. A process as claimed in claim 16(h), 23 or 24 wherein Z^8 is halo, C_1-C_4 alkanesulphonyloxy or C_1-C_4 alkylphenylsulphonyloxy.

26. A process as claimed in claim 25 wherein Z^8 is bromo.

27. A process as claimed in any one of claims 16 to 26 wherein X is O, NH, C_1-C_4 alkylene or C_2-C_4 alkenylene;
Y is C_1-C_6 alkylene;
R is H or C_1-C_4 alkyl;
R^1, R^2, R^3 and R^4 are each H;
one of R^6, R^7 and R^8 is -O(C_1-C_{15} alkyl), the alkyl of said -O(C_1-C_{15} alkyl) group being optionally substituted by aryl, and the remainder of R^6, R^7 and R^8 and R^5 and R^9 are each H;
R^{10} is COOH or $COOR^{11}$; and
"aryl" means phenyl optionally substituted by from 1 to 3 substituents each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CF_3, nitro and phenyl.

28. A process as claimed in claim 27 wherein X is O, NH, methylene, ethylene or ethenylene;
Y is propylene;
R is H;
one of R^6, R^7 and R^8 is -OCH_2(aryl) or -OCH(C_1-C_4 alkyl)(aryl) and the remainder of R^6, R^7 and R^8 and R^5 and R^9 are each H; and
R^{10} is COOH or COO(C_1-C_6 alkyl).

29. A process as claimed in claim 28 wherein X is methylene; R^7 is $-OCH(CH_3)(aryl)$ and R^5, R^6, R^8 and R^9 are each H; R^{10} is COOH or $COOC_2H_5$; and "aryl" means phenyl optionally substituted by 1 or 2 substituents each independently selected from n-propyl, isobutyl, methoxy, chloro, CF_3, nitro or phenyl.

30. A process as claimed in claim 29 wherein R^{10} is COOH and "aryl" means phenyl, 4-(n-propyl)phenyl, 4-isobutylphenyl, 4-methoxyphenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 4-trifluoromethylphenyl, 4-nitrophenyl or 4-phenylphenyl.

31. A process as claimed in claim 30 wherein "aryl" means 4-isobutylphenyl.

32. A process as claimed in any one of claims 16 to 26 which is used to prepare (R,S)-4-(3-[4-(1-[4-(2-methylpropyl)phenyl]ethoxy)-phenylethanoyl]indol-1-yl)butanoic acid or (S)-4-(3-[4-(1-[4-(2-methylpropyl)phenyl]ethoxy)-phenylethanoyl]indol-1-yl)butanoic acid: or a pharmaceutically acceptable salt thereof.

33. A process for the preparation of a pharmaceutical composition which comprises combining a compound of the formula (I), or a pharmaceutically acceptable salt thereof, which has been prepared by a process as claimed in any one of claims 16 to 32, together with a pharmaceutically acceptable diluent or carrier.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 92/01626

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 209/42 A 61 K 31/405

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 209/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
3 A	European Journal of Medicinal Chemistry, vol. 10, no. 2, March-April 1975, (Paris, FR), A. ALLAIS et al.: "Recherche d'analgésiques non narcotiques et d'anti-inflammatoires dans la série des carboxyalcoyl-1 acyl-3 indoles", pages 187-199, see page 194, table X, compounds with Ar=-CH=CH-	1
? A	EP,A,0458207 (FUJISAWA PHARMACEUTICAL CO., LTD) 27 November 1991, see claims (cited in the application)	1,8

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
19-08-1992	07. 10. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Natalie Weinberg

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 92/ 01626

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 13 and 14 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9201626 SA 62242

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 24/09/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0458207	27-11-91	AU-A- 7711691	21-11-91
		CN-A- 1056685	04-12-91